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THE AMERICAN REVIEW OF RESPIRATORY DISEASES

Clinical and Laboratory Studies of Tuberculosis and Respiratory Diseases

OFFICIAL JOURNAL OF AMERICAN THORACIC SOCIETY
MEDICAL SECTION OF THE NATIONAL TUBERCULOSIS ASSOCIATION

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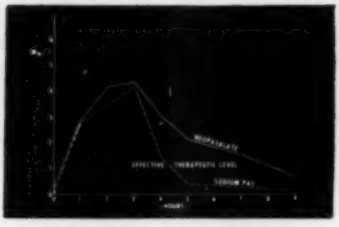

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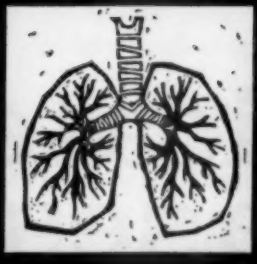

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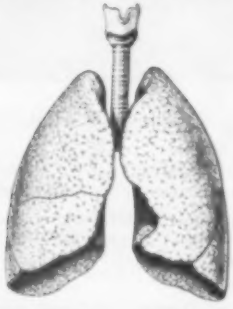

1. Duke, C. J.; Katz, S., and Donohoe, R. F.: Demethylchlortetracycline in the Treatment of Pneumonia, Read at Seventh Antibiotics Symposium, Washington, D. C., November 5, 1959. 2. Finland, M.; Hirsch, H. A., and Kunin, C. M.: Observations on Demethylchlortetracycline, Read at Seventh Antibiotics Symposium, Washington, D. C., November 5, 1959. 3. Hirsch, H. A., and Finland, M.: Antibacterial Activity of Serum of Normal Subjects After Oral Doses of Demethylchlortetracycline, Chlortetracycline and Oxytetracycline. **New England J. Med.** 260:1099 (May 28) 1959. 4. Lichter, E. A.; Sobel, S.; Spies, H. W.; Lepper, M. H. and Dowling, H. F.: Demethylchlortetracycline Therapy in Pneumonia, Scarlet Fever and Other Infections. **A.M.A. Arch. Int. Med.** 105:601 (Apr.) 1960.

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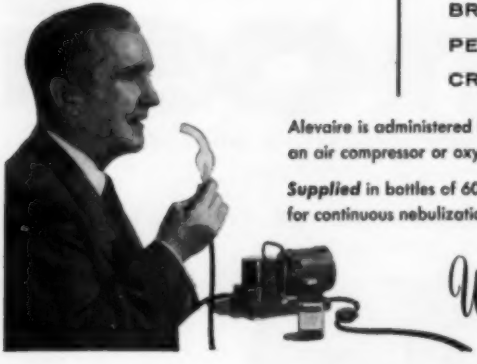

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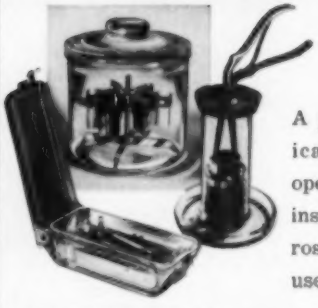

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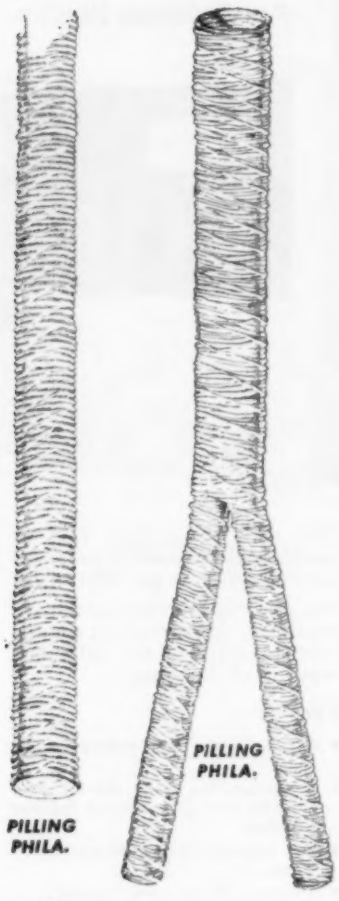

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1. DeBakey, M. E., Cooley, D. A., Morris, G. C., Jr., Collins, H.: Arteriovenous Fistula Involving the Abdominal Aorta, Annals of Surgery, 147:646 (May, 1958).

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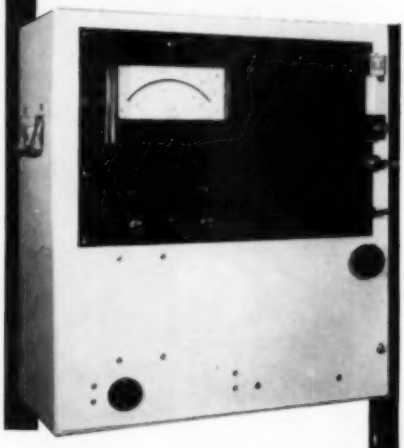

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In the May, 1960, issue of the REVIEW (volume 81, page 767), the second sentence of the Summary of the Note, "Antituberculous Activity of Rimino Compound of the Phenazine Series," by W. Steenken, Jr., *et al.*, should read: "The H37Rv strain *does not lose* its susceptibility to this compound when grown in medium containing subinhibitory concentrations."

In the June, 1960, issue of the REVIEW (volume 81, page 924), in the Note, "A New Antituberculous Amino Acid (α-Hydroxy-γ-Oxo-L-Norvaline)," by K. Kanazawa *et al.*, an error in the chemical identification of the amino acid appeared throughout the article. It should read "*Delta*-Hydroxy-γ-Oxo-L-Norvaline."

In the July, 1960, issue of the REVIEW (volume 82, Abstracts section, page 146), the abstract of the article, "The Electrocardiographic Pentalogy of Pulmonary Emphysema. A Correlation of Roentgenographic Findings and Pulmonary Function Studies." by R. R. Wasserburger *et al.*, is stated to have appeared in the November, 1959, issue of "Cardiology." The article actually appeared in the November, 1959, issue of *Circulation* (volume 20, pp. 831–841).

THE AMERICAN REVIEW
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Clinical and Laboratory Studies of Tuberculosis and Respiratory Diseases

VOLUME 82 | *October 1960* | NUMBER 4

THE J. BURNS AMBERSON LECTURE[1,2]

Aspects of Contemporary Research in Immunology

SIDNEY RAFFEL[3]

(Received for publication May 17, 1960)

The invitation to deliver a special lecture to this Society is of itself very gratifying, but the full flavor of the privilege lies in the fact that this lecture honors Dr. Amberson. Even those of us who have not had the good fortune to profit directly from his preceptorship have been inspired by more casual associations with him, and by hearing about his beneficent influence from those who have studied and worked with him. It is indeed a pleasure for me to present this fifth in the series of J. Burns Amberson Lectures.

Most of what I shall have to say will not be directly concerned with tuberculosis because I hope that it may interest some of you to have a summarized version of the status of prevailing thought in a few of the general areas of immunologic research. But such a departure does not leave considerations of tuberculosis behind; it is a striking fact that many of the currently exciting facets of immunologic investigation are grounded either in concepts derived from studies of tuberculosis, or upon techniques and procedures which have evolved from such studies, or which more directly employ the tubercle bacillus and its constituents for experimental purposes. Anyone who engages in the experimental study of tuberculosis soon comes to realize that this host-parasite relationship provides rich associations of this kind and that insights obtained from an understanding of the tuberculous process may help to clarify other areas of interest. Let me point out instances of this.

The *antibody response* during the course of tuberculosis, or in the vaccinated subject, is not a remarkable one in itself; in fact, it is apt to be rather subdued. But there are two interesting general points which attach to it. The first is of a negative kind and consists of the fact that acquired immunity in experimental tuberculosis constitutes the best documented example of a resistance which may be independent of circulating antibodies. I am not convinced that this conclusion has been established beyond doubt, since a negative conclusion is most difficult to rid of doubts. But its probability comes close to establishing a principle which gives us faith to pursue other instances of possible nonantibody immunity in infectious and noninfectious processes. Examples occur in the possible cellular mechanism of rejection of transplanted tissues and organs and in efforts to elucidate why patients with hypogammaglobulinemia, who are unable to manufacture appreciable quantities of antibodies (if any), nonetheless show heightened susceptibility to only a limited range of infectious agents (1).

In another connotation also, antibody responsiveness to the Mycobacterium is of much practical import in a variety of nontuberculous situations. Although, as I have mentioned, elaboration of antibody to the bacillus of infection is not outstanding, it is a curious fact that, if killed bacilli or a constituent isolated

[1] Founded and sponsored by physicians of the Bellevue Hospital Chest Service, New York, New York. The Amberson Lecture is delivered each year at the annual meeting of the National Tuberculosis Association and its medical section, the American Thoracic (formerly Trudeau) Society.

[2] Presented at the annual meeting of the National Tuberculosis Association and the American Thoracic Society on May 17, 1960.

[3] From the Department of Medical Microbiology, Stanford University School of Medicine, Stanford, California.

from them—the wax D or lipopolysaccharide—is presented to the tissues in an oily menstrum, the body is encouraged to produce excessive quantities of antibodies not only to the bacillary antigens themselves, but to whatever other antigens may be incorporated in such a mixture. In the United States this vehicle is referred to as Freund's adjuvant (2), and it is widely used in studies dealing with the nature of the antibody response, with the cellular origin of antibodies, and with the induction of pathologic states which apparently depend upon an immunologic process, such as experimental allergic encephalomyelitis, experimental thyroiditis, and other diseases.

The *hypersensitive* response is the second major immunologic facet of the tuberculous process. Needless to say here, the allergy of tuberculosis historically and by virtue of its striking characteristics has come to serve as a reference point for the entire category of delayed hypersensitivities, which are often referred to generically as hypersensitivities of "tuberculin type." A respectable amount of information has accumulated concerning the induction and characteristics of this kind of reactivity, and again we find this information being applied to the clarification of events in other areas. To cite an example, I may mention studies of contact reactivities to simple chemical substances of relatively well-known antigenic determinism, such as picryl chloride. Such substances induce delayed hypersensitivity when applied via the skin, but not when administered by any other systemic route, unless they are incorporated in Freund's adjuvant containing Mycobacterium or its wax D. This fact may supply the basis for an eventual understanding of the intrinsic mechanics through which such allergic states come about (3). Another example brings us again to the field of tissue transplantation. I have mentioned that rejection of normal tissue grafts may not be mediated by circulating antibodies, and those presently most concerned with studies of this phenomenon generally take the view that the tuberculin type of responsiveness determines rejection (4).

Through the work of Rich and others, we who are interested in tuberculosis were weaned away from the idea that delayed hypersensitivity is the mechanism of acquired resistance in this disease. It is most interesting to see a reanimation of this concept in relation to resistance to non-infectious, but in a sense parasitic, foreign tissue cells, and to realize that knowledge of tuberculin allergy serves as the premise for such studies and, reciprocally, that these studies may broaden our understanding of the implications of the tuberculin type of hypersensitivity.

This lengthy prelude is intended to establish the existence of a special kind of rapport between concepts and information gleaned from investigations of interactions between mycobacteria and their hosts and developing knowledge in other areas of immunology. This Society can hardly take credit for the properties of the bacillus and host which make their relationship so broadly significant, but it can congratulate itself upon the fact that through the years it has supported studies which have helped to bring some of the pertinent facets of this relationship to light. Having, I hope, made my point, I intend now to cast off from further reference to tuberculosis except by implication, and to discuss a sampling of the major lines of interest which currently engage investigators in immunology and related fields of investigation. The three aspects to be discussed deal first with the origin and nature of antibodies, then with facets of immunologic responses through the life span, and finally with a specific instance of antibody occurrence which may have special implications.

The Origin and Nature of Antibodies

All antibodies are globulins, and most of them are gamma globulins, although some appear to migrate electrophoretically with the faster moving β-fraction (5). Gamma globulins themselves constitute a heterogeneous collection of molecules, varying in molecular weight between 185,000 and something in the neighborhood of one million (6). All of these molecules may function as antibodies. It seems apparent now that most antibodies, perhaps all, originate in plasma cells. These cells, as you know, are not ordinarily found in the circulating blood and are present only in modest numbers in the tissues. They occur to some extent in lymph nodes and bone marrow, and most strikingly in lymphoid patches in the lamina propria of the gastrointestinal tract. But, after an antigenic stimulus, they appear in much larger numbers, and in a more actively synthesizing phase, in lymph tissues draining the site of antigen deposition. This alteration is especially impressive if

the antigen has been supplied along with tubercle bacilli or its wax in an oily vehicle, as mentioned before. A variety of direct and indirect evidence has established the importance of these developing plasma cells in the production of circulating antibodies, and I should like to make brief mention of some of this testimony.

(*a*) In a variety of disease states in which hyperglobulinemia occurs, as in sarcoidosis, cirrhosis, and other chronic hepatic diseases, in multiple myeloma and lymphomatosis, and in so-called "diseases of the globulins" in which large quantities of peculiar heavy globulins appear in the blood (7), plasma cells are generally found in higher than normal numbers. In some instances also there is an increased capacity to produce antibodies, as in some forms of hepatic disease. In a superficial correlative fashion, therefore, these observations suggest a relationship between numbers of plasmocytes and the production of globulins and antibodies.

(*b*) Clinical and experimental observations in a reverse situation lend more pointed support to this idea. In hypogammaglobulinemia there is a defect in the manufacture of gamma and sometimes of beta-2 globulins, and this is accompanied by a failure of synthesis of antibodies. The most constant histologic characteristic in these patients is a deficiency in plasma cells, not only under ordinary circumstances, but after application of the stimulus of injected antigen (8). Such patients have no "constitutional" defect which might preclude the appearance of antibodies in them, for in a clinical study in which slices of lymph node from a normal individual were inserted subcutaneously into a hypogammaglobulinemic one and a vaccine was applied, the subject developed circulating antibodies (9). The correlation of absence of plasmocytes with lack of gamma globulin and of antibody manufacture is so impressive in this disease as to supply excellent evidence of contingency of one upon the other.

(*c*) Studies with fluorescent antibody have provided inductive testimony in favor of the same conclusion. A few years ago Coons (10) demonstrated that antibody molecules can be tagged with a fluorescent substance (fluorescein isocyanate) without impairing their ability to react with the appropriate substrate. These antibodies can be visualized microscopically in whatever locale the reaction might be carried out. The usefulness of this general procedure has become so widespread, extending from the de-

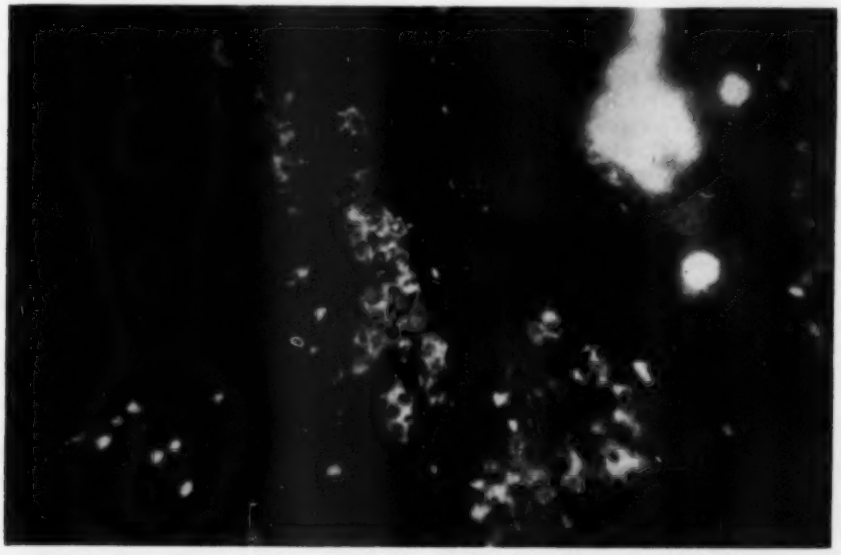

FIG. 1. Antibody producing cells (to diphtheria toxoid) in the medullary cord of a lymph node of a rabbit. The very bright area is an artifact. (*Courtesy of Dr. Albert Coons. Figure used with permission of the Journal of Experimental Medicine*)

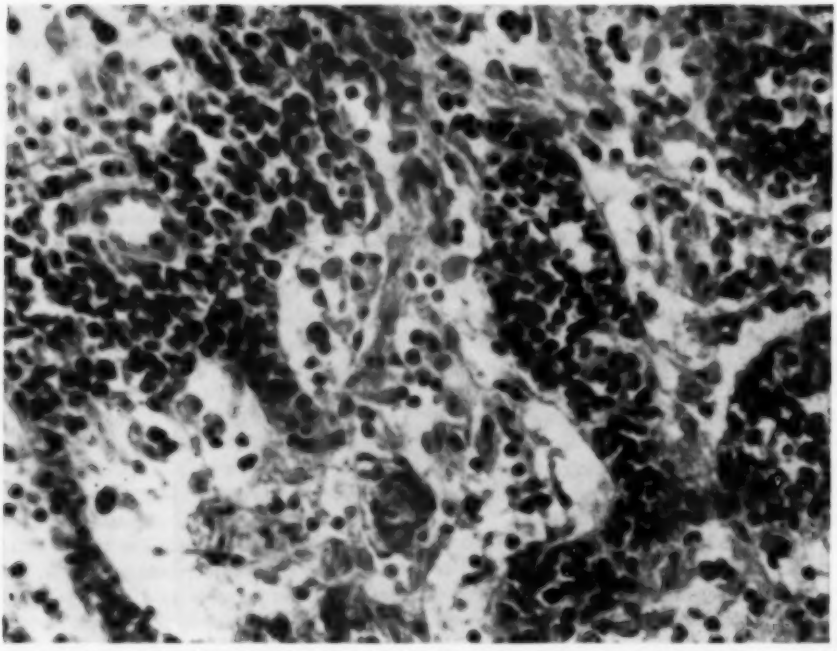

FIG. 2. Section of same lymph node shown in figure 1. Clusters of mature plasma cells in medullary cord. (Methyl green pyronine stain) (*Courtesy of Dr. Albert Coons. Figure used with permission of the Journal of Experimental Medicine*)

tection of bacteria in stool specimens and viruses in the tissues to endocrine secretions in glandular cells, as to warrant a series of expositions in its own right. For present purposes it is pertinent to describe one kind of experiment which Coons and his co-workers carried out with such marked antibodies (11).

A vaccinated animal was sacrificed during the time when antibodies were being synthesized, and histologic sections were made of the spleen and lymph nodes. To such sections a solution of antigen was applied. Antibodies in the sectioned cells attached to this and retained it; excess antigen was washed away. Fluorescent antibodies directed against the same antigen were applied to the tissue, and these in turn also attached themselves to the antigen. The net result of these maneuvers was the formation of a sandwich: cellular antibody, antigen, and fluorescent antibody. The last were detected microscopically in the precise areas of their attachment, as shown in figure 1. Sections were then stained with appropriate dyes to permit the identification of the cells showing fluorescence. These were for the most part plasmocytes, as shown in figure 2. Both of these illustrations were kindly supplied by Dr. Coons.

Such information derived from clinical observations and inductive investigations has led to the conclusion that plasma cells are of outstanding importance as synthesizers of circulating antibodies. If we pry into these cells to learn what goes on in the process of such synthesis, the plot thickens. It is apparent that antibodies are freshly made proteins; they are not refashioned from already existing molecules of globulin, but are put together anew from amino acids, and very quickly, within less than an hour after these have been supplied to the antibody-producing animal (12). The amino acids are thought to be lined up in appropriate sequence by ribonucleic acid and enzymes, and to condense into a polypeptide chain; this then may undergo a process of folding into the three-dimensional arrangement characteristic of the completed molecule.

This simplified version of the synthesis of antibody molecules may turn out to be correct in its essential features, but it does not take into account a question which is central to the real understanding of the antibody response and

related phenomena. The question is, how do cells which, perhaps for many years past, have been putting together a particular product—a plasma globulin—learn to make a protein which functions as antibody? The enzymatic retooling which might be required for this kind of alteration in the finished product would generally be thought of as being dependent upon changes in the fundamental directors of cellular activity, the genes; yet here it is apparently brought about by the rather bland process of exposing the tissues to a foreign antigenic substance. Furthermore, unlike a genetic mutation which would occur randomly, this alteration is very specifically directed.

For many years it has been supposed that the manufacturing cells can learn to make an altered protein under the impress of an antigen, although no one has been able to supply factual evidence as to how this kind of instruction may be imparted by the antigen (13). Recently, another school of philosophers has come to the fore to propose that antibody molecules are not the product of re-educated cells, but rather represent an increase in an entity which is already present in small quantity. This supposes that antigen stimulates the reproduction of cells which congenitally have been producing a protein at least approximating the structure of the appropriate antibody (14–16).

You may recall the historic Ehrlichian concept of the nature of the antibody response; this envisioned the existence on cells of a diversity of "side chains," some capable of combining with whatever foreign substance might find its way into the tissues. Following this combination the side chains were supposed to break off the cells and be destroyed. The cells in turn overcompensated for this injury by producing the same kind of side chains in so great an abundance that these overflowed into the blood stream and comprised specific antibody. The current viewpoint is essentially a more sophisticated restatement of this same concept.

Acceptance of the concept of antigenic selection of existing cells for proliferation and production of larger quantities of the antibody protein which the few parent cells were already synthesizing imposes the strain of imagining that each of us, as a birthright, possesses minute centers of response to an uncounted variety of foreign substances. On the other hand, the alternate view calls for a process of cellular instruction for which there is neither precedent nor clear model. Ingenious experiments are being applied to the question, but so far the choice between these ideas can be based only upon polemics; facts are not yet available.

Immunologic Activities through the Life Span

We are accustomed to thinking of the general ability of individuals to respond immunologically at different times of life in rather simple terms: whether they can or cannot, and during which periods. Thus, it is traditional to consider the first weeks of human life as a period of inability to respond to antigens. This deficiency is soon made good, so that pediatricians commonly begin to vaccinate infants between one and three months of age. Subsequent fluctuations in ability to produce antibodies may vary with individuals, but there seems to be no general biologic law pertinent to these fluctuations, unless it be that during old age antibody responses may be quantitatively decreased. There is not much evidence on this point, however.

Beginning several years ago, it has become increasingly evident that this comfortable view fails to encompass all of the circumstances pertinent to immunologic responsiveness. In addition to a state of positive responsiveness and indifference to antigens or negative responsiveness, there can be a negativity which is more than simple indifference; it is specifically inducible. The recognition of this state has extended the range of consideration of immunologic responsiveness beyond postnatal life back into the uterus or egg. This state is referred to as one of *immunologic tolerance*, and it can be brought about in the following way. If, during fetal life or in some instances during the neonatal period, an antigen is injected into a subject, it will ordinarily occasion no observable immunologic activity. But later, when the subject has attained a postnatal age at which it should respond to this antigen, injections of it are found to have no effect whatever, i.e., the animal has become tolerant to this antigen specifically. This state depends upon the "fact"—at least for descriptive purposes—that tissues exposed to a foreign substance at a time when they are not yet prepared to respond to it may go beyond ignoring it to the point of regarding it as congenial rather than foreign, and this lesson which the potentially

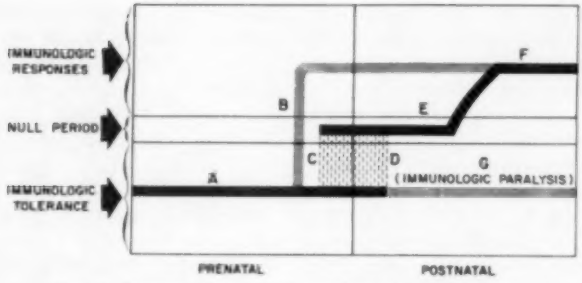

FIG. 3. Immunologic responses through the life span.

responding cells learn may remain to guide their activities in the future. Tolerance encompasses cellular reactivity as well as antibody formation.

Tolerance induction occurs most strikingly if the substance employed is not too far removed in its chemical and antigenic structure from the subject's own tissue makeup, as, for example, when the cells of one strain of animals are injected into a recipient of a related but incompatible strain (17). In this case the tolerance induced permits the treated subject to accept grafts from the original donor. An analogous situation may be created in adult subjects, generally by the administration of relatively large quantities of antigens; this is referred to as "immunologic paralysis." This was first investigated with the pneumococcal capsular polysaccharide as antigen in mice, on the basis of earlier observations by Felton of failures of some human subjects to respond to vaccination with this potent antigen (18, 19). Whether these two states have a common mechanistic basis remains to be seen; superficially, it would seem so, but various important details of the conditions under which they can be induced make this still an open question.

Taking these newer concepts into account, figure 3 is intended to illustrate all possible qualitative and quantitative fluctuations in immunologic responsiveness throughout the life span, beginning with the developing fetus. Three phases of reactivity are shown here: positive responsiveness; failure to respond, i.e., indifference or neutrality; and immunologic tolerance and paralysis. As shown, the response of the fetus is usually the inverted positive one of tolerance, and this circumstance pertains up to the time of birth or, in some animals, for a period after birth. There are, however, exceptions to this rule; some fetal animals can apparently respond positively, as exemplified by the fetal lamb which, at about the hundredth day of gestation (of a total period of one hundred and fifty days) is able to develop the ability to reject skin grafts, although it cannot produce humoral antibodies (20, 21). There is evidence also that the calf fetus may develop circulating antibodies to Leptospira (22).

This kind of exceptional activity on the part of the fetus is denoted by the broken line *B* which carries these limited examples into the phase of positive immunologic responsiveness prenatally. In general, however, there is a period of transition from the phase of inducibility of tolerance to the neutral period of indifference to antigens at about the time of birth, as indicated by the broad band between *C* and *D*. This null or neutral phase (line *E*) may now persist for variable periods until the subject acquires the ability to respond positively to antigens. As suggested by the slope of the line *E–F*, this acquisition is probably not an abrupt one in any single individual (23). The line then becomes horizontal again during postnatal life and, perhaps, as mentioned before, it may decline somewhat during old age. But this adult phase may also be interrupted by exposure to large quantities of antigen, in which case specific immunologic paralysis may intervene, as shown by line *G*.

These facets of response increase our awareness of potential and actual phenomena in a number of respects; for example, certain aspects of this information have been of great importance to the clarification of questions of antigenicity of tissues involved in grafting, and others may become equally important to a better understanding of the relative natures of apparently

different immunologic responses, i.e., antibody formation and delayed allergy induction.

Antibodies against Constituents of Cells

For years, immunologists have been fascinated by the idea that in certain circumstances an individual might respond immunologically against his own constituents to produce destructive disease, in violation of the "law" of self-preservation and of the immunologic axiom of self-recognition. In fact, an instance of this was described as early as 1904 by Donath and Landsteiner (24) in the case of paroxysmal hemoglobinuria, in which auto-antibodies against erythrocytes were found to be activated after chilling. About fifteen years ago it became established that many victims of acquired hemolytic anemia reveal auto-antibodies on their erythrocytes (25), and platelets may be similarly affected with resulting thrombocytopenic purpura. Currently, evidence is developing that many instances of chronic thyroiditis may also depend upon auto-antibodies, in this case directed against thyroglubulin (26, 27). There are other potential but as yet unproved examples of an analogous process; included among these may be rheumatoid arthritis and perhaps glomerulonephritis, nephrosis, and rheumatic fever.

I do not intend to go into the pros and cons of evidence on any of these situations now, but I would like to outline an aspect of one disease of possible immunologic origin because it brings up connotations of special interest. The disease is systemic lupus erythematosus. This is often accompanied by a number of exuberant immunologic activities, as suggested by hyperglobulinemia; the occurrence of auto-antibodies against erythrocytes, platelets, and leukocytes; the capacity to over-respond to foreign antigens; and the occurrence in most cases of the lupus erythematosus (LE) cell phenomenon (28). These patients have been known for some time to contain antibody-like entities directed against nuclear substances, and within the past year or two the nature of the response has become much clearer. It appears that antinuclear antibodies may be of four different kinds, one or more of which may be present simultaneously (29). One of these is probably directed against the crucial material of the hub of the cell, deoxyribonucleic acid. Another reacts with the basic protein associated with deoxyribonucleic acid, a third is directed against the total nucleoprotein complex, and a fourth constitutes a heterogeneous response to other nuclear components as yet undefined.

Whether or not these antibodies have to do with the etiology of lupus erythematosus is by no means certain; they may occur after the fact. If patients should for unknown reasons destroy their own cells, the antigenic substances liberated from nuclei might then induce these responses which have been so well studied. Whichever the case may be, whether auto-antibodies occasion the disease or vice versa, this pathologic entity provides one of the more thorough analyses now available of the scope and nature of anticellular antibodies in a human disease.

A point of much interest is contained in the suggestion that deoxyribonucleic acid may function as an antigen. If it be true that antibodies may develop against chromosomal substance, the prospects are opened that differences in gene composition may eventually become distinguishable on the basis of serologic specificity, and that germ cells might be selected experimentally by the application of immunologic procedures.

* * *

I have chosen to present to you a group of unrelated immunologic entities as representative of those areas of interest which most engage the attention of investigators at the present time. I suggest that, although these various studies have at the moment no particular relationship to our understanding of tuberculosis in the narrow sense, they form part of a body of knowledge and hypothesis to which studies of tuberculosis have contributed considerably and which, as they themselves develop, may on the other hand help to clarify issues with which many of us here are concerned.

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MINOR DISEASE IN TEN "HEALTHY" ADULTS[1, 2]

An Intensive, Day-by-Day, Clinical and Virologic Study

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Introduction

Acute disease of the upper respiratory tract is by far the most common cause of illness in the United States and is the leading cause of morbidity and lost man-hours in industry and in the military. Some reports credit the acute respiratory diseases with accounting for 30 to 50 per cent of all illnesses with a prevalence five to ten times greater than illness with the next highest morbidity (1). The main concern of industry and the military is the enormous amount of absenteeism that results from respiratory disease (1, 2). Although a large proportion of respiratory illness is mild and remains unreported (3), the majority of published reports on this subject have emphasized the economic burden in lost man-hours. These earlier studies, by reason of their retrospective nature, the large size of the populations studied, or because of their principal concern with disease causing absenteeism, have not weighed the burden of the truly minor illnesses which may go unremarked without daily and intensive observation and study.

Until recently, studies of minor respiratory diseases have also been handicapped by the virtual unavailability of specific diagnostic methods. The development in the last decade of new methods for the isolation and identification of viruses has resulted in the characterization of many "new" viral diseases of man (4, 5) and new opportunity for etiologic definition of minor illnesses.

The present study was undertaken with the dual purpose of assessing the true incidence of morbidity by daily and intensive clinical observation, and determining the number of illnesses now susceptible to etiologic definition through the use of optimal virologic methods and thrice weekly cultures for human respiratory viruses.

Materials and Methods

Subjects: The group studied comprised 5 men, aged thirty to fifty-one; five women, aged twenty-six to forty-three, all with professional or laboratory training and all associated with the activities of this laboratory. Eight of this group worked in this laboratory on a daily basis five to six days a week. One entered the laboratory almost daily but actually worked in a laboratory on another floor of the building. One male subject worked in this laboratory three days a week. These subjects were well aware of the purpose and methods of this study and were uniformly cooperative in giving details concerning daily symptomatology and specimens for virus isolation and serologic study. Four members of the group are writers of the present paper.

Of the men, one was single and four married. Three of the four married men lived in families with small children. All of the five women were single, one widowed and four unmarried.

Of this group, only one person had evidence of chronic disease. This individual, a woman, had rheumatic heart disease and a possible diagnosis of lupus erythematosus, although her activity was unimpaired. Three of the group, two males and one female, were subject to allergic rhinitis which had its onset in August and subsided in early October.

The environment: The laboratory in which—or adjacent to which—the subjects of this study worked contains six large rooms which are all interconnected. The work of the laboratory is concerned with research in respiratory viruses, but the bulk of the work consists of studies with egg-adapted strains of influenza virus which are demonstrably noncommunicable to man under ordinary circumstances (6). The failure of the present study to relate the majority of illnesses to any known viruses is adequate evidence that laboratory infection probably did not occur.

Method of fact gathering: One member of this group, a registered nurse, was in charge of the daily recording of symptoms. The interview technique was standardized by the use of a check sheet (figure 1) and in most instances interviews were conducted in private. Ample space under "Com-

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FIG. 1. Study sheet used for daily recording of clinical data.

ments" was allowed for any elaboration that might be necessary for the further characterization of a symptom. Care was taken that reporting of symptoms was uniform and painstaking, especially early in the study when symptoms which occurred frequently might be unreported (if not recognized as a symptom by the subject) or late in the study when a tendency to under-reporting was noted in those embarrassed by the frequency of symptoms.

For the purpose of this study, a *symptom* was considered to be any complaint offered by or elicited from the subject which represented a departure from comfort or physical well being, whether this deviation was objectively manifest or not, and even if frequently present in the subject.

Definition of what constituted a discrete illness was necessarily quite arbitrary. In cases of acute gastroenteritis, this diagnosis readily presented itself in recognizable symptom patterns and offered little difficulty. Greater difficulty was encountered in the definition of a discrete respiratory illness. A respiratory illness was considered to have occurred if the symptoms of an individual differed substantially in their intensity, quality, or number from the usual pattern of respiratory symptoms in that individual. Illnesses thus defined were usually set off by clear temporal limits. Difficulty arose when an acute respiratory illness was engrafted on an existing chronic respiratory symptom, such as post-nasal discharge due to mild chronic sinusitis. In such instances, the decision was based on the clinical judgment of the senior author (M. M.) who followed the course of all subjects throughout the study.

Baseline observations of morning and afternoon temperature and pulse rate were made in all subjects to establish their normal patterns. After the baseline observations were completed, such entries were omitted from the daily record unless, because of the nature of an illness or complaint, such observations were deemed necessary.

Laboratory procedures: The laboratory procedures employed were carefully selected as being optimal for the diagnosis of virtually all recently

recognized viral infections of the human respiratory tract, including *adenoviral infections, parainfluenza 1 and 3, Coxsackie viral infections of the Group B type*, and *herpes simplex*. Although throat swab materials are not optimal for the isolation of most enteroviruses (poliovirus and ECHO virus), these agents are not considered to be primary or important causes of respiratory tract symptoms in the adult and, if present, should have been detected by the monkey kidney cell cultures used. Monkey kidney cell cultures are inferior to chick embryo inoculation in the isolation of influenza viruses (7); however, chick embryo amniotic sac inoculation was also employed whenever serologic evidence suggested the possibility of influenza, e.g., subject *No. 10*.

The tissue culture methods employed were not optimal for the detection of the J.H. or 2060 virus.

Bacteriologic studies were considered unnecessary on the basis that bacterial pathogens appear to contribute insignificantly to the total of minor respiratory illnesses (8). The afebrile gastrointestinal illnesses encountered were not associated with severe dysentery, and similarly were not subjected to bacteriologic study.

Thrice weekly pharyngeal swabbings were obtained from each individual and were either inoculated promptly into HeLa cell or monkey kidney cultures or frozen at −70°C. prior to such inoculation. When indicated by the nature of symptoms, conjunctival specimens and anal swabs were obtained.

The HeLa cell cultures were grown in a growth medium consisting of 10 per cent horse serum in mixture 199. The maintenance medium for HeLa cells comprised 7.5 per cent chicken serum, 25 per cent tryptose phosphate broth, and 67.5 per cent 199 (9). This same maintenance medium was also used as a collection medium for specimens.

Second-passage monkey kidney tissue was obtained by trypsinization and grown in 32-ounce serum bottles, using 0.5 per cent lactalbumin hydrolysate and 5 per cent horse serum in Earle's buffered saline solution as a growth medium. When an adequate sheet of cells had grown out, cells were removed from the bottles by incubation with ethylenediaminetetra-acetic acid tetrasodium salt (Versene®) for thirty minutes at 36°C., then seeded into tissue culture tubes. Mixture 199 alone was used as the maintenance medium.

Following inoculation, cultures were observed daily for the presence of cytopathic effects and, in addition, the recently described hemadsorption test (10, 11) was performed approximately every five days, using 0.2 ml. of a 0.4 per cent suspension of human "O" cells. Four tubes were inoculated per specimen and were held from 2 to 4 weeks following inoculation before they were termed negative. If any suspicion of cytopathic effect or hemadsorption was observed, a further passage was made. With certain specimens, amniotic inoculation of the 11-day-old chick embryo was also undertaken.

Complement-fixation tests were performed according to the procedure outlined by Lennette, using 2 units of complement and 2 units of antigen (12). For influenza A and B viruses, the Asian strain (Jap. 305) and B/G1/54 strain, respectively, were used in the form of allantoic fluid virus and thus were chiefly viral antigen.

Hemagglutination-inhibition tests employed an inhibitor-sensitive A2 (Asian) strain following treatment of sera with periodate (13, 14), and also the B/G1/54 strain of influenza B virus with trypsin-inactivated sera (14).

Results

General considerations of symptom patterns: It was surprising to find that within this group of ostensibly healthy persons the average number of symptom-free days per person was 120 of the 266 total days, representing 45 per cent of the observation period (table 1). Thus, more often than not, the average subject in this group was symptomatic. Although the extremes of the percentage of symptom-free days among individuals varied widely (6 to 78 per cent), the median figure was 48 to 49 per cent and the rate for most subjects was close to the 45 per cent mean figure of the group as a whole.

Establishment of undue prevalence of group symptomatology by comparison of average numbers of symptoms per month for each individual with observed monthly incidence: Because the symptom-free state was uncommon in most subjects, it was important in assessing undue or epidemic prevalence of symptoms in the group as a whole to compare the average (baseline) symptom rate

TABLE 1

Calculation of Number of Symptom-free Days per Person

Total Number of Days—266

From September 8—May 31

Subject	Age	Sex	Number of Symptom-free Days of 266 Total Days	Per Cent of Time Symptom-free
1	38	M	63	24
2	51	M	208	78
3	38	M	202	76
4	29	M	151	57
5	35	F	37	14
6	34	F	129	48
7	30	F	109	41
8	27	F	153	58
9	43	F	16	6
10	34	M	131	49
Average.....			119.9	45

TABLE 2*a*

MONTHLY INCIDENCE OF TOTAL SYMPTOMS OF EACH SUBJECT

	1	2	3	4	5	6	7	8	9	10	Total/ Month
September	52	36	28	4	25	25	17	7	100	11	305
October	89	9	10	37	67	10	42	19	163	60	506
November	71	7	8	84	52	25	20	20	105	15	407
December	42	8	0	4	46	61	51	10	109	43	374
January	70	0	24	25	96	22	34	23	89	53	436
February	68	6	22	29	88	22	12	16	71	44	378
March	73	0	23	11	95	43	17	25	83	12	382
April	59	6	2	15	112	34	33	29	114	56	460
May	40	3	47	22	57	7	35	17	93	46	367
Total	564	75	164	231	638	249	261	166	927	340	3,615

TABLE 2*b*

RATIO OF TOTAL NUMBER OF SYMPTOMS IN A GIVEN MONTH TO THE AVERAGE NUMBER OF SYMPTOMS PER MONTH ESTABLISHED DURING THE 9-MONTH STUDY PERIOD

	1	2	3	4	5	6	7	8	9	10	Per Cent with > Average
Average Number per Month	63	8	18	26	71	28	29	18	103	38	
September	0.8*	4.5	1.6	0.2	0.4	0.9	0.6	0.4	1.0	0.3	20
October	1.4	1.1	0.6	1.4	0.9	0.4	1.4	1.1	1.6	1.6	70
November	1.1	0.9	0.4	3.2	0.7	0.9	0.7	1.1	1.0	0.4	30
December	0.7	1.0	0.0	0.2	0.6	2.1	1.8	0.6	1.1	1.1	40
January	1.1	0.0	1.3	1.0	1.4	0.8	1.2	1.3	0.9	1.4	60
February	1.1	0.8	1.2	1.1	1.2	0.8	0.4	0.9	0.7	1.2	50
March	1.2	0.0	1.3	0.4	1.3	1.5	0.6	1.4	0.8	0.3	50
April	0.9	0.8	0.1	0.6	1.6	1.2	1.2	1.6	1.1	1.5	60
May	0.6	0.4	2.6	0.8	0.8	0.3	1.2	0.9	0.9	1.2	30

* <1.0 = less than average number of symptoms.

per month established by analysis of the entire 9-month study of an individual with the observed symptom-incidence for the individual in any given month. This relation of the number of symptoms observed in any given month (table 2*a*) to the average monthly incidence may be expressed as a ratio indicative of increase or decrease from average incidence. In table 2*b*, monthly variations from "normal" of the symptoms of each individual subject are so expressed. Thus, each subject serves as his own control. Analysis of the deviation of the group as a whole from average symptom prevalence is indicated in the extreme right-hand column of the table as per cent of subjects per month with average symptomatology. Thus, in the initial month of the study, only 2 of 10 subjects (20 per cent) had, for them, above-average symptom prevalence, while in the following month 70 per cent of the subjects were unduly symptomatic.

Study of the constancy of individual symptom patterns: The suggestion that certain individuals, such as subjects *Nos. 1* and *9* (table 2*a*), were constantly burdened with more symptoms than their fellows was investigated further. After termination of the laboratory studies, daily recording of symptoms was continued for an additional 7 months in all but one subject. These additional data permit comparison for each person of his symptom incidence during 4-month periods (September-December) of 2 successive years. Although this particular period includes September, which greatly influenced the seasonal rhinitis in the 3 allergic subjects, the constancy

of relative symptom incidence among members of the study group was remarkable. In figure 2 the average symptom incidences per month for each subject in both 1958 and 1959, September-December periods, are plotted. This figure demonstrates not only the constancy of the symptom incidence for each person in the two different years, but also the constancy of his position in the group in terms of relative symptom incidence.

Symptoms referable to the respiratory tract: Slightly less than 50 per cent of all symptoms reported involved the respiratory tract. The incidence of such symptoms in each subject is detailed in tables 3*a* and *b*. Undue prevalence of respiratory symptoms is again expressed as a ratio, utilizing *average* prevalence for the individual (as in table 2*b*). The major contribution of respiratory symptoms to the total number of symptoms is illustrated in figure 3, in which the percentages of individuals with above-average respiratory and total symptoms are compared for each month. It will be noted that the percentage of respiratory symptoms fluctuated very closely with total symptomatology. On the average, for the entire observation period, respiratory symptoms contributed 47 per cent of all symptoms. Respiratory symptoms included only those complaints which were directly referable to the upper respiratory passages (nasal discharge and congestion, sore throat, et cetera) or lower respiratory tract (hoarseness, cough, et cetera). In the tabulation of these symptoms, no distinction was made between those occurring during a definite

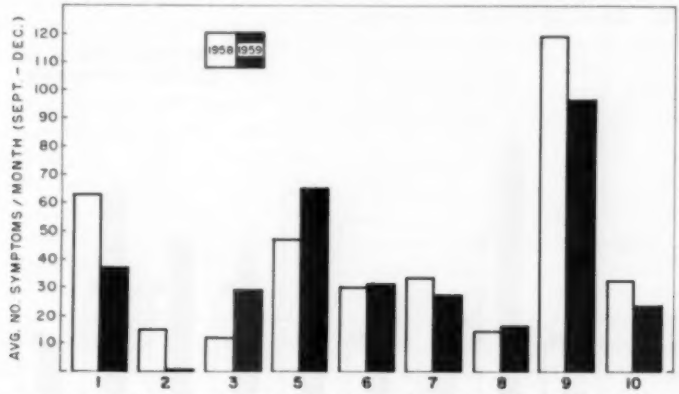

FIG. 2. A comparison of the average monthly incidence of symptoms in 9 subjects (Nos. *1–10*) in two successive years.

TABLE 3*a*

INCIDENCE IN SUBJECTS OF SYMPTOMS REFERABLE TO THE RESPIRATORY TRACT

Subject Number	1	2	3	4	5	6	7	8	9	10	Total/Month
September	24	36	26	0	23	18	17	0	24	1	169
October	52	9	4	3	44	5	32	5	48	4	206
November	40	4	2	39	35	2	4	1	20	0	147
December	33	7	0	3	31	51	23	1	23	19	191
January	36	0	14	6	64	17	18	5	28	32	220
February	55	6	20	17	49	12	2	3	16	30	210
March	22	0	15	8	69	40	13	17	3	10	197
April	27	2	0	4	74	15	8	5	45	34	214
May	13	1	26	8	44	0	4	0	40	28	164
Total	302	65	107	88	433	160	121	37	247	158	1,718
Average per month	34	7	12	10	48	18	13	4	27	18	

TABLE 3*b*

RATIO OF NUMBER OF RESPIRATORY SYMPTOMS IN A GIVEN MONTH TO THE AVERAGE NUMBER OF RESPIRATORY SYMPTOMS PER MONTH ESTABLISHED DURING THE 9-MONTH STUDY

Subject	1	2	3	4	5	6	7	8	9	10	Per Cent of Subjects per Month with > Average Symptomatology
September	0.7*	5.0	2.0	0.0	0.5	1.0	1.3	0.0	0.9	0.1	30
October	1.5	1.3	0.3	0.3	0.9	0.3	2.5	1.3	1.8	0.2	50
November	1.1	0.6	0.2	3.9	0.7	0.1	0.3	0.3	0.7	0.0	20
December	1.0	1.0	0.0	0.3	0.6	2.9	1.8	0.3	0.9	1.1	30
January	1.1	0.0	1.2	0.6	1.3	0.9	1.4	1.3	1.0	1.2	60
February	1.6	0.8	1.1	1.7	1.0	0.7	0.2	0.8	0.6	1.7	40
March	0.6	0.0	1.3	0.8	1.4	2.2	1.0	4.3	0.1	0.6	40
April	0.8	0.3	0.0	0.4	1.5	0.8	0.6	1.3	1.7	1.9	40
May	0.4	0.1	2.1	0.8	0.9	0.0	0.3	0.0	1.5	1.6	30

* <1.0 = less than average number of symptoms.

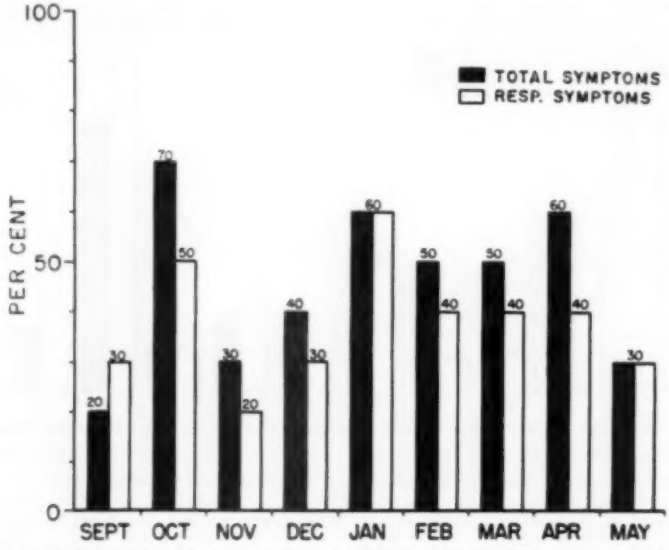

FIG. 3. The concordance of respiratory and total symptomatology. The proportion of subjects who manifested undue prevalence of respiratory and total symptoms in each month. Percentage of subjects with above-average number of symptoms per month compared with percentage with above-average respiratory symptoms, 1958–1959.

respiratory illness and those presenting as isolated minor complaints. Neither were concomitant constitutional symptoms of a specific respiratory illness included.

Seasonal allergic rhinitis and respiratory symptomatology: The effect of seasonal allergic rhinitis on the pattern of respiratory and total symptoms in the "allergic" subjects, *Nos. 2*, *3*, and *6*, is clearly revealed in tables 2 and 3. The high incidence of symptoms during the month of September in these subjects stands in contrast to their relative freedom from complaints in the two succeeding months. Indeed, it is interesting but inexplicable that this later low incidence of respiratory symptoms in these subjects coincided with a period (in October) of suddenly increased respiratory symptomatology in all subjects.

Symptoms referable to the gastrointestinal tract: Although gastrointestinal symptoms constituted only 6 per cent of all symptoms, those of the gastrointestinal tract were the next most troublesome group in contributing to specific illness and absenteeism. Symptoms involving systems other than the respiratory and gastrointestinal tract were rarely the cause of specific illness, but were usually associated with respiratory or gastrointestinal disease, or occurred as completely isolated and transient complaints. One exception to this was the very high incidence of ocular symptoms in subject *No. 9*. These symptoms were probably induced by drug therapy of her underlying chronic disease.

Absenteeism: An inspection of the rate of absenteeism from work provides a guide to the nature of this experimental study group in that a low rate of absenteeism is presumptive evidence of good general health and absence of hypochrondriasis. Although the average subject in this group was symptom-free less than half of the time, the average absenteeism per person was only 1.5 days during the 266-day period of this study. Three subjects were not absent at all. The range of absenteeism was 0 to 4 days. In only one case was absence from work longer than one day for any illness; and, in this one case, the total period lost was 3 consecutive days. Thus, with the entire group of 10 persons, a total of 15 days from work was lost; 11 of these 15 days were lost from work because of respiratory symptomatology, and 4 were related to gastrointestinal disease.

Nature and incidence of discrete episodes of respiratory illness: Those symptom complexes which represented, according to the criteria (*see* Methods), discrete episodes of respiratory disease varied in number from 2 to 10 per person for a mean of 4.5 per person during the 266-day study period (table 4). It may be seen from figure 4 that the incidence of upper respiratory infections follows the usual seasonal variation with peaks in December, January, and February. The average duration of symptoms for all respiratory infections was 8.1 days with a range of 4 to 13.3 days. There was no indication that infections occurring during the winter months were any more severe or prolonged than those occurring at other times. If, within the temporal limits of this study, the number of subjects per month who experienced acute respiratory disease for the first time are determined, it may be seen that the attack rate is represented by a gradual slope, with an increase of 2 new infections per month so that by January all 10 subjects had experienced at least one infection (figure 5).

No epidemiologic relationship between transient nonspecific symptoms in individuals of this group to the presence of distinct respiratory disease in one of its members could be discerned. Minor transient complaints seemed to be constantly present in the group and bore no quantitative relationship to major outbreaks of respiratory infections; nor could they be grouped into

TABLE 4

CALCULATION OF THE NUMBER OF DISCRETE ACUTE UPPER RESPIRATORY TRACT DISEASES

Subject	Number of Respiratory Illnesses	Months								
		S	O	N	D	J	F	M	A	May
1	10	2	1	1	1	1	1	1	1	1
2	2				1		1			
3	4					1	1	1		1
4	3			1		1	1			
5	7	1	1	1	1	1	1	1		
6	5			1	1	1		1	1	
7	4		1		1	2				
8	4					1	1	1	1	
9	3		1		1				1	
10	3				1				1	1
Total	45	3	4	4	6	9	6	5	5	3
Average per person	4.5									

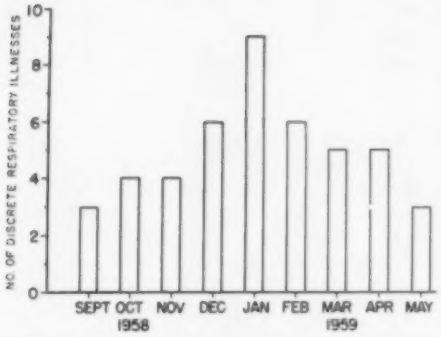

FIG. 4. The monthly incidence of discrete respiratory illnesses in the study population of 10 subjects.

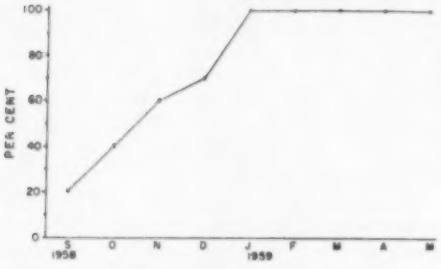

FIG. 5. The cumulative incidence (per cent of subjects involved) of first attacks of discrete respiratory illness in the study group.

seasonal peaks, although most of the minor complaints were respiratory in nature.

In table 5 the percentage incidences of the various respiratory and ancillary symptoms are presented. Malaise was a prominent complaint and accounted for 70 per cent of all symptoms associated with discrete respiratory tract disease. Pharyngeal and nasal complaints, as expected, were the most common specific symptoms recorded in sufferers with upper respiratory disease. The low incidence of associated gastrointestinal symptoms is similar to that observed with influenza (15).

It is commonly observed that during the course of an acute respiratory disease certain symptoms are more pronounced and troublesome for a given individual than others. Although some respiratory infectious agents tend to stimulate more or less characteristic signs and symptoms, e.g., adenovirus and epidemic influenza, these signs are by no means pathognomonic and may also be induced by other agents (16).

Individual variation in symptom response to respiratory infection: In the study of the symptoms of respiratory disease affecting this group, some subjects appeared unduly vulnerable to the repeated occurrence of certain symptoms. Subject *No. 1* had 10 respiratory infections and experienced ocular complaints in 7 of these episodes. Symptoms or evident lesions of herpes simplex occurred in 2 subjects, with an incidence of 30 and 14 per cent, respectively. Hoarseness occurred in 4 subjects; in one, three times and in another twice. Cervical lymphadenopathy occurred in 3 subjects; one experienced this reaction in each of his 3 respiratory infections.

Relation of menstruation to respiratory illness: In the 5 female members of the group, a careful record was kept of the onset, duration, and termination of menstruation. In these subjects there were 23 respiratory infections; 16 of these infections (70 per cent) occurred at or after the mid-point of the cycle, and 9 of these had their onset in the last quarter or pre-menstrual period. Although these figures are highly suggestive that respiratory symptoms are more apt to appear between menstrual periods and particularly during the latter half of the menstrual cycle,

TABLE 5

MANIFESTATIONS OF DISCRETE RESPIRATORY DISEASE LISTED IN ORDER OF FREQUENCY

Non-specific (constitutional)	Percentage Incidence
Malaise	72.8
Headache	52.0
Fatigue	51.6
Feverishness	46.4
Specific (localized)	
Pharyngeal (sore throat, pain on swallowing)	93.6
Nasal (congestion or discharge)	81.0
Cough (nonproductive)	47.0
Myalgia	33.5
Ocular (burning eyes, retro-orbital pain)	31.0
Laryngeal (hoarseness)	22.1
Chest pain (related to coughing)	17.3
Gastrointestinal (loss of appetite, nausea, and/or vomiting)	17.0
Cervical lymphadenopathy	15.0
Recurrent labial herpes simplex	4.4

it is below the level of significance as determined by the chi-square test, even though 50 per cent fewer infections occurred at the time of menstruation than could be expected if chance alone were operating. Further studies of this nature may be able to demonstrate some correlation. It is interesting to note that in controlled investigations in the transmission of the common cold virus to volunteers, the female appeared more susceptible to the acquisition of infection in the premenstrual period (17).

Relation of recurrent herpes simplex to respiratory illness: There were only 2 subjects in this group (subjects *Nos. 1* and *5*) who suffered from recurrent herpes simplex during the study period. One had 4 episodes and the other 5. The average period between attacks was 30 days, with a range of 20 to 42 days and 19 to 40 days, respectively. The infection usually involved the mucocutaneous margin of the lips and the anterior portion of the nose.

The effect of respiratory illness on the appearance of herpetic lesions was investigated in these 2 subjects. In subject *No. 1*, a male, who had 5 herpetic attacks, 3 of these occurred just previous to the onset of an upper respiratory infection. One occurred during an infection (3 days after onset) and only one was unrelated to any clinically evident disease. Subject *No. 5*, a female, had 4 attacks, 2 of which occurred 5 and 3 days, respectively, before the appearance of a respiratory infection. One occurred during an infection (5 days after onset), and a fourth was not related to any clinical disease.

Therefore, 5 of the 9 episodes of herpes in this group of subjects occurred just previous to (1 to 5 days) the development of respiratory symptoms. It has been well documented that the "agent provocateur" of recurrent herpetic lesions can range from slight physical trauma to grossly disturbed physiologic states. The appearance, then, of recurrent herpes in these 2 subjects just previous to the onset of illness might represent a subtle indication of minor disturbances of host physiology before the appearance of symptoms; or might have been the only evidence of an abortive illness in the instances unassociated with disease. The possible *causal* role of the herpes simplex virus in the genesis of the respiratory illnesses is belied by the failure to isolate the virus from other than local vesicular sites.

Nature and incidence of gastrointestinal diseases: Although gastrointestinal symptoms contributed only 6.0 per cent to the total symptoms of the group, nevertheless, they were the second most common cause of discrete illness and absenteeism, accounting for 27 per cent of the total days lost. The average number of cases of enteritis per person for the entire observation period was 1.8. An average of 2 cases occurred per month.

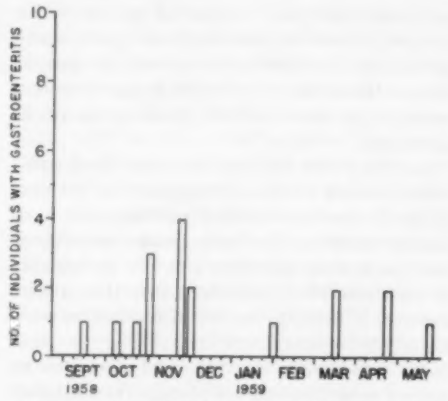

FIG. 6. The weekly incidence of discrete gastrointestinal illnesses.

In figure 6 the monthly incidence of enteritis in the study group is recorded. In the first week of November, 3 cases of enteritis appeared within a 5-day period; each attack lasted one to 2 days. Following this, there was an absence of any new cases until the end of the third week and the beginning of the fourth week of the same month. At that time, 4 more cases appeared, one of which constituted a "second attack," occurring in an individual who was ill for only one day in the first week of November. The next week there were 2 more new cases and then no further disease until the first week in February.

The occurrence of 9 cases of enteritis (affecting 8 different subjects) within one month was further differentiated from the previous and following episodes of gastroenteritis by definite clinical features. The other cases recorded in this study had an average duration of 3.1 consecutive days without remission. The intensity of the diarrhea or vomiting was usually severe. In contrast to this, in the November outbreak, the duration of illness was 4.5 days. The symptoms were not consecutive but, rather, punctuated with remissions ranging from one to 5 days which occurred in 5 of the 9 cases. Diarrhea, although present, was mild in nature. Particularly distressing were the hyper-

peristalsis and mild abdominal cramps which occurred. Constitutional symptoms, particularly malaise, were at times quite marked, but appetite was usually maintained. No febrile reactions were recorded, nor were there any striking changes in pulse rate.

In spite of the inability to isolate the responsible organism *in vitro*, investigations of the syndrome of acute nonbacterial gastroenteritis have clearly established the epidemiologic and clinical features of these infections (18, 19). A diagnosis of viral enteritis is consistent with this present outbreak. Clinically, the salient features, as mentioned above, were the absence of fever, the presence of low-grade diarrhea, and moderate to marked constitutional symptoms. The spread of infection was rapid. Assuming high hygienic practices of the subjects of this group, the high attack rate would suggest either an agent of high communicability or a remarkably susceptible population. In this particular instance, it seems valid to conclude that a single agent should be held responsible; nevertheless, attempts to isolate a viral agent from the throat and the rectal swabs inoculated on monkey kidney and HeLa cells met with failure.

Laboratory Studies

Virus isolation studies: A total of 439 throat and 11 rectal swabbings were inoculated into monkey kidney and HeLa cell cultures. Of this total, 75 of the throat swabbings and the 11 rectal specimens were selected from instances of overt illness. The remaining 364 throat swabbings were obtained during periods of relative health. These studies did not result in the demonstration of cytopathic agents or of agents detectable by the hemadsorption test (*see* Methods).

Serologic studies: These studies comprised complement-fixation tests with the following antigens: influenza A and B viruses; adenovirus, type 4; and hemadsorption viruses, types 1 and 2 ("para-influenza" 3 and 1, respectively) (20).

These serologic studies were performed on all sera collected at monthly intervals from the 10 subjects of this study. Two positive results were obtained: (*1*) a rise in complement-fixing and hemagglutination-inhibiting antibody to influenza B virus was observed in one of the male subjects (*No. 10*) in October, 1958, before the nation-wide prevalence of influenza B was noted; (*2*) subject *No. 1* experienced a serologically demonstrable adenoviral infection in October, 1958, in association with a pharyngitis with lymphadenopathy. In spite of these symptoms, the subject had no febrile response. It is of interest that this subject suffered from a mild conjunctivitis in association with this illness. However, the significance of this abnormality as a specific feature of an adenoviral infection is unclear in this individual as he suffered from similar ocular complaints in 7 of his 10 respiratory illnesses, in which there was no serologic evidence of adenoviral infection. The clinical picture of the subject who suffered from influenza B was remarkable in that no respiratory complaints had been elicited. The main features of his illness were constitutional symptoms, namely, headache, myalgia, and loss of appetite. These complaints were severe but resulted in absence from work of only one day.

Discussion

The most striking finding of the present study is the latent but finite load of misery borne more than half the time by 10 "healthy" people without manifest disruption in their productivity and efficiency. But what measure do we have of their efficiency other than their ability or inability to drag themselves through the day's routine—their "absenteeism" or "non-absenteeism"? Clearly then, either the normal are not healthy or the healthy are diseased more often than not, as evidenced by measurable deviations from well-being. It would be difficult to derive a definition of health from the present study. In many instances the presence of definite but mild and unrelated symptoms offer no recognizable patterns of specific disease. In such instances, there was little objective derangement of host physiology; nevertheless, it is reasonable to assume that the "state of health" of the individual was compromised or at least open to challenge. Thus, the subjects of this study were frequently either in a state of incipient disease or definitely suffering from illness definable as an unusual occurrence of multiple symptoms. If, then, the health records of the 10 subjects in this study seem atypically poor, the same cannot be said of their capacity to function adequately in the pursuit of their duties when this capacity is judged by their low rate of absenteeism. Thus, illness provided no evident gain or release from obligations.

The undramatic but awesome contribution of

acute inflammatory disease of the respiratory tract to total symptomatology is again documented in the present study with the occurrence of 2 to 10 "colds" per person during a 9-month period.

The epidemiologic inferences from observations of these respiratory illnesses are difficult to assess. It would appear from the presence of multiple illnesses in the same individual, e.g., subjects *Nos. 1, 5,* and *6,* that many infectious agents were introduced into this population. Therefore, the indolent onset of respiratory illness in the group as a whole may be interpreted as evidence of considerable population resistance to the multiple agents introduced or may imply the introduction into this population of agents characterized only by low-grade communicability. It may be more reasonable to suggest variation in host susceptibility as the dominant factor in shaping these epidemiologic patterns of respiratory disease in this study group. The importance of the host in shaping clinical response to infection and the suggestion that respiratory disease symptomatology may be conditioned more by the subject than by the infectious agent is evidenced by the liability of certain subjects to certain recurrent symptoms, such as conjunctivitis or laryngitis, during several discrete episodes of illness. That certain individuals may experience "more than their share" of all types of illness which may cause lost time from work has been previously noted (21). The subtle interaction between changes in human physiology and minor disease is further suggested by (*1*) the apparent increased incidence of "colds" in the intermenstrual female and (*2*) the appearance of herpes simplex infection *before* the overt manifestation of respiratory disease.

This study has shown that the significance of symptoms must be interpreted with reference to the background of symptomatology which may be peculiar to an individual. This background can be defined only by intensive daily observations and an investigation of the patient's previous response to minor infectious disease. This is probably particularly true for adults in whom time has allowed the establishment of mild but chronic illness and correspondingly altered reaction patterns. Subject *No. 1* with a history of chronic sinusitis frequently was subject to acute complications of this disorder following acute respiratory illness. Certainly, in this individual, such symptoms as headache, ocular pain, and cough accompanying a respiratory disease might well reflect the exacerbation of latent but chronic respiratory disease and mechanical obstruction rather than primary involvement of the specific anatomic sites suggested by the symptoms associated with the new acute infection. This possibility is further suggested by the longitudinal observation that this patient responded uniformly to discrete respiratory illnesses with qualitatively the same symptom pattern. From another aspect, the presence of a respiratory symptom in subject *No. 3* gains significance from the fact that he was apparently devoid of any complaints 78 per cent of the time. With the foregoing considerations in mind, it is believed that the technique of daily clinical observation, although elaborate and time-consuming, is the only method at present by which the broad spectrum of clinical manifestations of disease, particularly mild respiratory disease, can be validly investigated.

The failure of viral isolation in the present study stands in contrast to attempts to define acute febrile respiratory disease in children (22), but parallels studies of large metropolitan and college populations with respect to respiratory disease and virus etiology. In such studies, the yield of cytopathic agents relative to the number of individuals and respiratory illnesses has been quite small (23, 24). There is some evidence that para-influenza viruses may induce a milder disease in adults than in children (25). If this milder illness results from pre-existing specific immunity, recovery of virus from such adult patients might be compromised. It is also probable that currently available cell culture methods are inadequate for cultivation of many of the etiologic agents of afebrile respiratory infection.

Summary

An intensive study of 10 "healthy" young adults during a nine-month period has demonstrated: (*1*) a surprisingly high frequency of minor symptoms, as revealed by careful daily questioning; (*2*) the occurrence of approximately 7 discrete minor illnesses per person, the majority of them involving the upper respiratory tract; (*3*) the afebrile nature of these illnesses and the low rate of absenteeism associated with them; and (*4*) a failure to categorize by the best of current virologic methods any but 2 of these illnesses.

The findings of this study indicate that the

burden of minor disease is perhaps even greater than previously suspected; that most of it continues to defy etiologic definition; and that absenteeism, in a highly motivated group of people, may be a poor guide to the incidence and severity of such disease.

Sumario

La Enfermedad Banal en Diez Adultos "Sanos." Intenso Estudio Clínico y Virológico de Día en Día

Este intenso estudio de 10 adultos jóvenes "sanos" durante un período de nueve meses ha puesto de manifiesto: (1) una frecuencia sorprendente por lo alta de pequeños síntomas que revelara un interrogatorio cuidadoso; (2) la existencia de unas 7 enfermedades discretas de orden menor por persona, la mayoría de las cuales afectaban las vías aéreas superiores; (3) la naturaleza afebril de estas dolencias y el bajo índice de absentismo a que dieron lugar; y (4) el fracaso en la clasificación de todas estas enfermedades, aparte de 2 de ellas, con los mejores métodos virológicos corrientes.

Los hallazgos de este estudio indican que la sobrecarga impuesta por la enfermedad leve quizás sea hasta mayor de lo sospechado hasta ahora; que la mayor parte de ella continúa evadiendo la definición etiológica; y que el absentismo, en un grupo de personas inspiradas por altos motivos, tal vez constituya un guía inadecuado en lo tocante a la incidencia y gravedad de dicha enfermedad.

Resume

Forme mineure de maladie chez 10 adultes "en bonne santé." Une étude clinique, virilogique, intensive, journalière

Cette étude intensive de 10 jeunes adultes "en bonne santé," pendant une période de neuf mois, a montré: (*1*) une fréquence étonnamment grande de symptômes mineurs révélés par un interrogatoire soigneux journalier; (*2*) la découverte d'à peu près 7 maladies discrètes par personne, la majorité d'entr'elles interessant les voies respiratoires supérieures; (*3*) la nature afébrile de ces maladies et le taux bas d'absences en relation avec elles; et (*4*) l'échec à les classer dans une catégorie par les meilleures méthodes virologiques courantes, exception faite pour 2 de ces maladies.

Les données de cette étude indiquent que le "fardeau" des maladies mineures est peut-être même plus grand que cela n'avait été prévu auparavant; que la plupart d'entr'elles continue à défier toute définition étiologique; et que les absences chez un groupe de gens de très bonne volonté peut être un guide de mauvaise qualité en ce qui concerne la fréquence et la sévèrité d'une telle maladie.

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VIRUS STUDIES IN CHRONIC BRONCHITIS[1]

IAN JACK AND BRYAN GANDEVIA

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INTRODUCTION

Exacerbations of chronic bronchitis, defined as an increase in cough and in volume and purulence of the sputum without evidence of pneumonia or bronchopneumonia, are often preceded by symptoms of an upper respiratory tract infection. Serologic evidence of infection with influenza (1, 2) and, in a few instances, adenoviruses (3–5), has been noted in some hospital inpatients investigated during exacerbations of chronic bronchitis. Exacerbations of chronic bronchitis, often severe but without roentgenographic opacities, were encountered in association with proved infection by the virus of Asian influenza (6). In the present paper, the results of virus studies are presented, using both cultural and serologic methods, in a series of outpatients with chronic bronchitis observed over a year (1958).

PATIENTS AND METHODS

Largely on a basis of their ability and willingness to collaborate, 19 patients (14 males and 5 females) were chosen for an investigation of the natural history of bronchitis. The detailed clinical and bacteriologic observations will be the subject of a separate report. All of the patients had persistent cough with sputum which, at least for some part of the year's observation, was purulent or mucopurulent; in all, a bacterial pathogen or potential pathogen (*H. influenzae* in 14 cases) was isolated from the sputum in one or more cultures. Preliminary chest roentgenograms, with bronchograms if indicated, together with roentgenograms during severe exacerbations, were obtained to help in excluding other diseases and pneumonic or bronchopneumonic complications. The exercise tolerance of the patients ranged from normal to the inability to walk more than 50 yards on the flat; several had reversible bronchoconstriction of varied severity.

[1] From the Department of Pathology, Royal Children's Hospital, and the University Department of Medicine, Royal Melbourne Hospital, Victoria, Australia.

The patients were first seen late in 1957. The virus studies began in February, 1958, and continued for twelve months. Four patients died in the winter of 1958. The virus investigations consisted of attempts at isolation of viruses and the performance of serologic tests.

The patients were given sealed jars containing sterile saline and were instructed to gargle with this solution at the slightest indication of an upper respiratory infection, or upon any increase in wheezing or in the volume or purulence of the sputum. At all of the interviews, the importance of early gargling was stressed. In spite of these efforts, gargling was occasionally forgotten or left too late (perhaps, more particularly, when antecedent upper respiratory symptoms were denied) while, on the other hand, some specimens were taken when symptoms were negligible or, at least, failed to develop into a genuine exacerbation of bronchitis. On clinical grounds, it was believed that more than half of the specimens were taken at an appropriate time and were associated with minor and, in some cases, severe exacerbations of bronchitis. Gargle specimens were stored at 4°C. until delivered to the laboratory, usually within one or two days, when the patient was also interviewed. A total of 62 specimens was obtained from 16 subjects.

Venous blood was taken for serologic tests from each patient on admission to the study and thereafter approximately quarterly. Additional specimens were taken at the onset of alleged exacerbations, and again three weeks later. The regular specimens were obtained in case subclinical infections occurred, perhaps without exacerbations of bronchitis (2). In all, 138 specimens of blood were collected; these were stored at −20°C. until tested as a series.

All of the gargle specimens were inoculated into monkey kidney cell cultures which were examined up to six days for the presence of viral cytopathogenic effects. These cultures were also examined for the presence of hemadsorption (using human erythrocytes) in the absence of cytopathogenic effects. Twenty-six selected gargle specimens were "blind-passaged" into monkey kidney cell cultures and both observations were repeated. Twenty representative specimens were inoculated into tubes containing HeLa cells. In the known absence of epidemic influenza, 6 specimens only were inoculated into sixteen-day-old chick embryos.

Complement-fixation tests were carried out on all serum specimens for influenza A, influenza B

(using group-specific "S" antigen in each instance), and adenoviruses (using group-specific antigen prepared from a HeLa cell pool of types 2, 3, and 7). Initially, a screening test was applied to all serum specimens in an attempt to identify those deserving full titration but, as they proved unhelpful, representative serum for each patient was titrated in full. In those patients with significant amounts of adenovirus antibody, all specimens were titrated. Serum was tested at an initial dilution of 1:8; those specimens reported below as negative had no complement-fixing antibody at this dilution.

Results

The number of gargle specimens received each month is indicated in table 1. The monthly distribution was influenced by the death of 4 patients in July, thus reducing the number of contributors thereafter to 15. No specimens were received from 3 patients, and only one was received from each of 3 other patients: in 4 instances the patients' ability to cooperate was misjudged. One patient died in his first exacerbation, and the sixth patient, with mild symptoms, claimed to have had no exacerbations although pus cells and *H. influenzae* were transiently identified in the sputum. In spite of these factors, the slightly greater prevalence of upper respiratory symptoms during the winter months of June, July, and August is probably real and is in accord with previous experience of the prevalence of acute respiratory disease in Melbourne.

All attempts at virus isolation failed. No cytopathogenic effects were detected in any of the cultures and no hemadsorption was found.

The serologic findings may be summarized by saying that no change in levels of antibody to influenza A or B was observed in any of the patients with significant antibody titers. No patients showed a fourfold increase in adenovirus antibody titer. Significant adenovirus antibody levels were found in 10 instances, but in no case was a significant fluctuation in level demonstrable when all specimens were titrated.

TABLE 1

Number of Gargle Specimens Received Each Month

	1958											1959
Month	2	3	4	5	6	7	8	9	10	11	12	1
Number of gargle specimens.	2	7	7	5	8	11	8	4	5	1	2	2

Discussion

The presence of antibodies to influenza A and B and to adenovirus in about half of the patients reflects past experience with these viruses, and no evidence was found of infection acquired during the year of observation. No influenza epidemic occurred during the year, nor were the epidemic varieties of adenovirus (types 2, 3, 4, and 7) prevalent. Sporadic adenovirus and ECHO virus infections were recognized during the year. None of the former occurred in this series; evidence of ECHO infection was not specifically sought. Similarly, although four waves of croup and unidentified upper respiratory tract infection were noted at the Royal Children's Hospital, one of which occurred in June, the study yielded no croup-associated viruses; these would have been detectable by the hemadsorption technique.

Some interest attaches to the fact that the 4 deaths in the series occurred within a few weeks of one another, all following an acute exacerbation of bronchopulmonary symptoms. No autopsy material was obtained for investigation in the present study, but no virus isolations were made from an unusual number of cases of presumed viral infection, involving the respiratory tract, which were seen at the Melbourne city morgue during the months of June, July, and August (7). The occurrence of these severe cases does not favor the "common cold" as the initial cause of the simultaneous exacerbations in the patients of the present study.

The writers are unaware of any comparable study of patients with chronic bronchitis over a period of time. The failure to demonstrate evidence of viral infection in the presence of unequivocal exacerbations may mean that exacerbations are related to infections caused by unidentified viruses, including the common cold (8), but some exacerbations are unassociated with antecedent upper respiratory symptoms. Further elucidation of the problem may require detailed study of illnesses in the families of patients with chronic bronchitis.

Summary

From 19 patients with chronic bronchitis observed for a year, 62 gargle specimens were obtained at the onset of symptoms referable to

the upper respiratory tract, together with 138 blood samples, including "acute" and "convalescent" specimens as well as regular quarterly samples. Virus isolation and serologic techniques failed to reveal evidence of infection with influenza A and B viruses, adenoviruses, hemadsorption or croup-associated viruses during the year of observation, in spite of clinical evidence of exacerbations of bronchitis.

Sumario

Estudios de Virus en la Bronquitis Crónica

De 19 enfermos que tenían bronquitis crónica y observados un año, se obtuvieron 62 ejemplares de gargarismos en la iniciación de síntomas imputables a las vías aéreas superiores, junto con 138 muestras de sangre, comprendiendo ejemplares "agudos" y "convalecientes," así como las habituales muestras trimestrales. Las técnicas de aislamiento de virus y serológicas no revelaron signos de infección por los virus de influenza A y B, adenovirus o virus asociados con hemadsorción o crup durante el año de observación, a pesar de los signos clínicos de exacerbaciones de la bronquitis.

Resume

Etudes virales dans la bronchique chronique

A partir de 19 malades porteurs de bronchite chronique observés pendant un an, 62 échantillons de gargarismes furent obtenus au début de symptômes se rapportant aux voies respiratoires supérieures, en même temps que 138 échantillons de sang, comprenant des échantillons "aigûs" et "convalescents" aussi bien que des échantillons réguliers trimestriels. L'isolation virale et les techniques sérologiques ne purent mettre en évidence une infection par les virus A et B de l'influenza, des adenovirus, des virus "hemadsorption" ou associés au croup, pendant l'année d'observation, en dépit de l'évidence clinique d'exacerbations de la bronchite.

Acknowledgments

The patients who participated are to be commended for their cooperation and their ready acceptance of the inconvenience involved. The writers are grateful to those colleagues mentioned in the references for permission to quote their experience, and are also indebted to Miss H. Ellis, Sister K. King, and Mrs. Joan Dwyer for technical and administrative assistance.

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EPIDEMIOLOGIC STUDIES OF OBSTRUCTIVE VENTILATORY DISEASE OF THE LUNG[1]

I. A Review of Concepts and Nomenclature

JOHN R. GOLDSMITH

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Introduction

When the same thing is called by different names or different things by the same name, confusion is bound to result. Such is the case at present with a group of chronic, nontuberculous, nonmalignant conditions of the lung including asthma, bronchitis, and emphysema. The present series of papers suggests a new generic name for a discrete group of these chronic diseases of the lungs, and illustrates the utility of such a name for epidemiologic studies of these diseases. Methods used, difficulties encountered in such studies, and the pattern of results are to be reported.

Nomenclature

A disease called chronic bronchitis is a leading cause of death and of certified sickness disability in Great Britain. The prevalence of the disease in other North European countries and in the United States of America is a great deal lower, according to reported statistics. The reasons behind this difference are baffling. Fletcher (1) and Oswald (2) have pointed out one possible reason. In Great Britain, when a man dies, having coughed for a number of years and having produced abundant sputum, even though he may have had the symptoms and signs of asthma and pathologic findings which are consistent with pulmonary emphysema, the death nevertheless is usually ascribed to chronic bronchitis. The idea is current in Great Britain that chronic bronchitis is a cause of pulmonary emphysema and asthma among adults. The certified causes of death, thus, do not usually indicate the latter two conditions but do indicate the former. In the United States and perhaps in some North European countries, the finding of pulmonary emphysema is usually not believed to indicate the presence of an underlying disease. For these reasons, among others, a review of the terms used for this group of diseases seems indicated.

A number of principles of nomenclature may be used when attaching names to diseases and conditions. The name may be descriptive, anatomic, physiologic, or etiologic. In the case of diseases of the heart, the simultaneous use of these principles is well established. In the group of diseases under consideration, which are usually coded in the United States vital statistics under the names asthma, bronchitis, pulmonary emphysema, bronchiectasis, and chronic interstitial pneumonia, a variety of these principles of nomenclature has been used. Asthma, for example, is derived from the Greek word meaning panting and is a descriptive name. Emphysema is a pathologic name. As used here, it means what has been called chronic obstructive or hypertrophic pulmonary emphysema. Bronchitis is an anatomic term, implying inflammation. As used here, the term means bronchitis other than acute. Bronchiectasis is likewise an anatomic term. The name chronic interstitial pneumonia is chiefly a pathologic term, but not a very explicit one. That anatomic, physiologic, and etiologic diagnoses have not yet been simultaneously used in diseases of the lung reflects our relatively scanty knowledge about diseases of that organ. A major consideration in the naming of disease entities is that the name should have some meaningful relationship to the clinical situation and to the prognosis. For this purpose, however, the terms should define a uniform group of cases which have a common clinical picture and a common prognosis. The proposal discussed in the present paper attempts to meet these requirements.

It is therefore proposed that the name "obstructive ventilatory disease of the lung" be applied to a group of disorders which are characterized by symptoms, signs, and laboratory tests which indicate ventilatory obstruction. For brevity, the term obstructive disease will sometimes be used in the remainder of these papers.

[1] From the Department of Public Health, State of California, Berkeley 4, California.

Symptoms

The common symptom of this group of diseases is shortness of breath on exertion, provided the shortness of breath is not due to cardiovascular disease. Shortness of breath is so commonly believed to indicate heart disease that it seems quite likely that many persons with obstructive disease have been and are being erroneously diagnosed. This disorder may coexist with heart disease, in which case clinical examination and laboratory studies would indicate the true state of affairs. The dyspnea associated with this disorder is to be distinguished from that occurring in heart disease by the fact that true orthopnea (dyspnea occurring only lying down) is not usually associated with it, even when the dyspnea is severe. Cough is usually present at some stage in the disorder but is not essential to it. Sputum, although often present, is also not essential.

Physical Findings

Among the physical findings, few are of decisive value. The wheeze of asthma, the hyperinflation of emphysema, and the rales of bronchitis are common, but of little help in defining a uniform disease entity. Fletcher (3) has shown that agreement on the physical findings in emphysema is difficult to reach even when two skilled observers perform physical examinations on the same subject. In advanced cases, physical findings of pulmonary hypertension or right heart failure may be found.

Laboratory Findings

Physiologic laboratory findings are the essential criteria of this proposed disease entity. It is necessary to demonstrate that the timed vital capacity, the maximal breathing capacity, the maximal expiratory flow rate, or related tests deviate significantly from the expected values before obstructive disease may be said to be present.

The maximal breathing capacity test is the oldest of the tests available for the detection and evaluation of this group of disorders. The principal disadvantages of the test are that it is strenuous to perform and difficult to standardize (4, 5). It is generally thought that each laboratory using the maximal breathing capacity test must determine its own standard or normal value since test techniques may cause so much variation in the results (6). In introducing a simple automatic device for determining, during a single expiration, both the volume of gas expelled during a brief period at the start of expiration and the vital capacity, Gaensler (7) has made possible the rapid and relatively comfortable testing of a large number of people. In the development of the "air velocity index"[2] which provides a criterion for distinguishing obstructive from restrictive or mixed ventilatory impairment, Gaensler (8) has also provided a description of the concept of obstructive disease. His principal concern in developing this concept, as well as the instrument for measuring it, appeared to be to assist in the selection of surgical candidates with pulmonary tuberculosis and other disorders. Gaensler's concept should be applied more widely. When expressed as a ratio to the total vital capacity, the timed vital capacity[3] (the volume expelled during a brief period of time in early expiration, usually one second) has the advantage over most lung function tests in that it is possible to establish values which are substantially independent of age, sex, and physique in populations without disease (9, 10).

The principal advantage of the maximal expiratory flow tests, using instruments developed by Goldsmith (11, 12) and by Wright (13) is that the equipment is quite compact and easily portable. The accomplishment of these tests is somewhat less strenuous for the subject than either of the other two tests. However, there is but a small difference between the maximal expiratory flow tests and the timed vital capacity in regard to the difficulty for the subject. A number of variations on this type of test have been proposed, such as

[2] The "air velocity index" is the ratio of the per cent of predicted normal for the maximal breathing capacity (MBC) for that subject to the per cent of predicted normal for the vital capacity (VC):

$$\frac{\text{observed MBC/predicted MBC}}{\text{observed VC/predicted VC}} = \text{air velocity index}$$

When this value exceeds 1.2, the subject is said to have "restrictive" ventilatory disease; when it is less than 0.8, "obstructive" ventilatory disease is said to exist. When the observed values are less than 80 per cent of the predicted, but the index is between 0.8 and 1.2, a "mixed" ventilatory defect is said to be present (8).

[3] The phrase "timed vital capacity" is widely used. Recently the use of "forced expiratory volume in . . . seconds" has been recommended. It is to be abbreviated FEV_1, FEV_2, $FEV_{0.5}$, et cetera.

the maximal midexpiratory flow (14) and the expirogram (15, 16), both of which are based on the reading of a graph inscribed by a spirometer during forced expiration. The obtained set of values is then interpreted by comparison with standards for such tests.

Three Types of Obstructive Disease

On the basis of the most prominent symptoms and signs, obstructive ventilatory disease may be classified into three types: the *bronchitic* type, the *asthmatic* type, and the *emphysematous* type.

In the persons with the bronchitic type, cough and sputum predominate. Often there is relatively little shortness of breath. The physiologic test values obtained from persons in this group are likely to be nearer to the values expected for persons who are not ill than for persons in the other two groups.

Persons with the asthmatic type are the easiest to detect since the subjects present either wheezing or the characteristic musical dry, rales of asthma.

The person with the emphysematous type exhibits shortness of breath on exertion as the major symptom. Patients with the emphysematous type may or may not show asthma, rales, cough, or sputum; but they invariably have dyspnea on exertion. By contrast, patients with the asthmatic type may have little or no fixed shortness of breath but present episodic dyspnea. Some patients with bronchiectasis, acute bronchitis, and chronic interstitial pneumonia may have no ventilatory obstruction; such cases would not be included in this entity. However, patients with a severe form of each of these three conditions often show an element of ventilatory obstruction.

Any clinician who deals with this group of diseases recognizes that there is substantial overlap among these three types. Persons most closely resembling the bronchitic type may have an increased anteroposterior chest diameter and hyperresonance of the lung. They may, from time to time, show the high-pitched musical rales of asthma. The widespread use of compound diagnostic terms such as *asthmatic bronchitis* and *emphysema with bronchitis* is evidence of this overlap.

Natural History

Nevertheless, it is possible to recognize a general natural history that includes most of the symptom patterns and signs in this group of diseases. The onset is usually related to acute episodes of "bronchitis" with cough and sputum. Characteristically the cough becomes more protracted with repeated bouts of bronchitis until, in fact, the cough becomes continuous, increasing in severity during episodes of infection which may occur several times a year.

Gaensler and Lindgren (17) reported a retrospective study of patients with emphysema. Prior to the study they thought that most of the patients they saw with pulmonary emphysema had "dry emphysema," that is, without cough and sputum. In reviewing histories of patients with emphysema selected from an alphabetical sequence, 68 per cent had chronic bronchitis with emphysema; 18 per cent had "wet emphysema"; and 14 per cent had "dry emphysema." By chronic bronchitis they meant cough and expectoration preceding dyspnea three years or more, worse in winter, in mornings, and worse with fog, dust, and smoke. This study suggests that "bronchitis" may play a larger part than was thought in the natural history of the emphysematous type of obstructive ventilatory diseases of the lung.

Occasionally, the infection is severe and becomes a manifest pneumonia. Indeed, in the preantimicrobial era this was probably a common cause of death for patients with this syndrome. Today, however, these infections are usually treated successfully, and the subjects may, after several years, ultimately develop the manifestations of emphysema with right heart failure and carbon dioxide retention which is the characteristic terminal episode. It is quite possible that a number of patients with the diagnosis of acute pneumonia have obstructive disease.

The onset of obstructive disease may be an attack of asthma. This is usually not a type of asthma which is clearly related to inhalation allergy, but is more likely to be characterized as "intrinsic asthma." The initial attack may be followed by isolated episodes of shortness of breath and wheezing; only with the passage of some time are shortness of breath and wheezing likely to persist. Under these circumstances, the evolution from the "asthmatic" to the "emphysematous" type may be insidious.

Sometimes patients with obstructive ventilatory disease are first recognized in the emphysematous stage; such patients, however, often give a history of cough or respiratory infection, or of the protracted inhalation of respiratory tract irri-

tants, such as cigarette smoke or occupational dust or fumes.

Mortality Data

Mortality data for the group of obstructive diseases indicate their growing importance. The group of conditions has shown a rising mortality rate. In California, for example, the rise was almost 300 per cent for pulmonary emphysema in the period from 1950 to 1958.

The rise in deaths, shown in table 1 and figure 1, certified the causes included in the obstructive ventilatory disease group for the years 1950 to 1958 in California, and is compared with the respiratory tuberculosis death data. By 1953, the lines of the graph had crossed. The bulk of the increase has been in pulmonary emphysema. The increase in emphysema has been so great, in fact, that it suggests an epidemic of chronic disease. Part of the increase may be related to increased familiarity with and use of the diagnosis by physicians. There are other explanations which should be considered as well, such as migration to California of persons with the disease, or survival of persons formerly succumbing to pneumonia or tuberculosis. These possibilities must be investigated before concluding that all of the increase is real.

Despite the difficulty of selecting the correct diagnosis to be put on the death certificate and the possible inadequacies of coding, the data in table 1 do not support the view that deaths are being certified as due to emphysema which formerly had been certified as due to other diagnoses in this group. Although the California data do not show this, the death rate from emphysema, nationwide, is greater in cities than in rural areas (18). In Great Britain, Fairbairn and Reed (19) and Stocks (20) have presented careful statistical studies which indicate a relationship of mortality from chronic bronchitis to fog and urban air pollution.

Air Pollution and Obstructive Disease of the Lung

Increasing concern about the consequences to health from the breathing of polluted air gives added importance to the concept of obstructive

TABLE I

Deaths and Death Rates due to Selected Respiratory Diseases
California, 1950–1958

Respiratory Disease	1950	1951	1952	1953	1954	1955	1956	1957	1958
Total selected respiratory diseases									
California, total	910	1,014	1,214	1,331	1,433	1,498	1,736	1,978	2,279
Rate	8.6	9.2	10.3	10.9	11.4	11.5	12.8	14.0	15.4
Asthma									
Deaths	336	369	479	491	442	422	460	467	398
Rate	3.2	3.3	4.1	4.0	3.5	3.2	3.4	3.3	2.7
Emphysema[1]									
Deaths	161	196	257	341	392	459	592	803	926
Rate	1.5	1.7	2.2	2.8	3.1	3.5	4.4	5.7	6.3
Bronchitis[2]									
Deaths	413	449	478	499	599	617	684	708	955
Rate	3.9	4.1	4.1	4.1	4.8	4.7	5.0	5.0	6.5
Respiratory tuberculosis									
Deaths	2,114	1,982	1,654	1,275	1,115	991	937	829	806
Rate	20.0	17.9	14.3	10.6	8.9	7.6	6.9	5.8	5.5

[1] Emphysema with bronchitis is included with emphysema.

[2] Bronchitis includes acute bronchitis, bronchitis unqualified, chronic bronchitis, bronchiectasis, and other chronic interstitial pneumonia.

Note: Death rates are per 100,000 population.

Sources: U. S. Bureau of the Census, *United States Census of Population: 1950*, Volume II, *General Characteristics of the Population*, California.
State of California, Department of Finance, Population Estimates, 1951–1958.
State of California, Department of Public Health, Death Records.

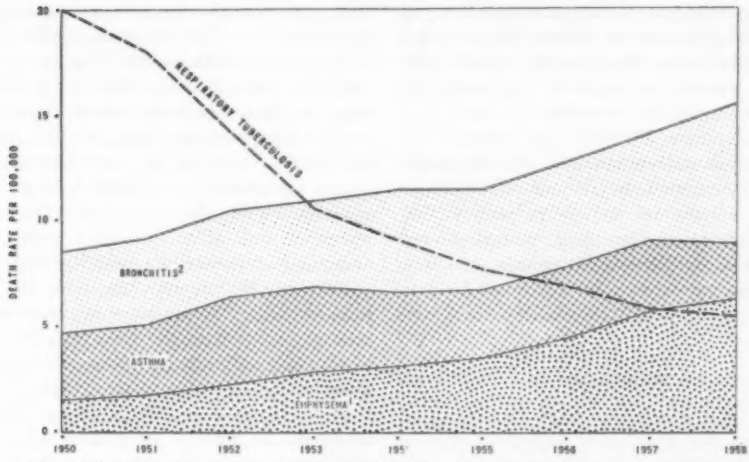

FIG. 1. Death rates due to selected respiratory diseases, California, 1950–1958.

[1] Emphysema with bronchitis is included with emphysema.

[2] Bronchitis includes acute bronchitis, bronchitis unqualified, chronic bronchitis, bronchitis, bronchiectasis, and other chronic interstitial pneumonia.

Sources: U. S. Bureau of the Census, *United States Census of Population: 1950*, Volume II, *General Characteristics of the Population*, California.
State of California, Department of Finance, Population Estimates, 1951–1958
State of California, Department of Public Health, Death Records.

ventilatory disease. Sources of polluted air to which the lungs may be exposed include community air pollution, the toxic gases, vapors, and fumes to which occupational exposure occurs, and the inhalation of cigarette smoke. Examples relating these sources to the etiology of obstructive ventilatory disease may be cited. Gough (21) and his associates have shown the relationship of coal-workers' pneumoconiosis to focal pulmonary emphysema; the relationship of silicosis to emphysema is well established; allergic bronchial asthma is closely related to the inhalation of pollens; the inhalation of cadmium fumes (22) has been associated with pulmonary emphysema, both in man and experimental animals. Hammond and Horn (23) and Dorn (24) have shown that the mortality from this group of diseases was much higher among cigarette smokers than among nonsmokers. Flick and Paton (25) have shown the association of cigarette smoking with low values for maximal flow in a group of hospitalized males. Whether this group of diseases is related to the community air pollution common in California metropolitan areas is yet to be determined. Its relation to air pollution in Great Britain has been well established.

Information about the dosage levels of the various types of pollution would be of the utmost importance. Further work will be needed on this problem.

Other Etiologic Factors

The role of allergic responses to the inhalation of pollens and dusts is widely accepted in bronchial asthma. There is a growing body of data concerning the role of repeated infection in producing pulmonary emphysema (26). In addition, there has been experimental work which suggests that emphysema may be produced by changes in bronchial circulation (27). With the passage of time, other etiologic factors may arise and their importance be demonstrated. Such work is likely to depend in part on the results of epidemiologic studies.

Previous Epidemiologic Studies

An early study was that of Pemberton and MacLeod (28), who conducted a survey of men more than 40 years of age living in a rural area of Massachusetts. A history, physical examination, and a one-second vital capacity test were obtained for each patient. Pemberton's study showed the

association of tobacco smoking with this group of diseases and also with an abnormal one-second vital capacity ratio. Higgins (29) studied the symptom pattern, occupational and smoking history, and ventilatory function in a number of population samples. He found an invariable increase in cough and sputum in smokers compared with that in nonsmokers. The one-second forced expiratory volume was used as an index of ventilatory obstruction. Groups of smokers showed lower ventilatory capacities than groups of nonsmokers. Among smokers, no significant decrease in function occurred with increasing tobacco consumption.

Discussion

It may be of small importance to the patient with obstructive ventilatory disease whether or not he is thought to have—say—asthma, or the asthmatic type of obstructive disease. But prevention of the occurrence or progression of illness such as this depends on studies of groups of affected persons from whom accurate histories can be obtained. For the success of such epidemiologic studies, random samples from homogeneous groups of such persons will need to be studied.

Using present nomenclature, the following dilemmas arise:

Asthma, as commonly used, includes asthmatic children, persons with a cardiac basis for their wheezes, as well as older persons with severe irreversible dyspnea. Clearly, this is not a homogeneous group of persons.

Emphysema may be defined by physiologic tests, such as residual volume, in addition to tests useful for defining obstructive disease; but the residual volume tests are difficult to use with the large numbers of persons usually needed for epidemiologic studies. There remains some disagreement on the clinical and laboratory bases for the diagnosis.

Chronic bronchitis is rather a vague diagnosis in the minds of many physicians; it is readily confused with acute conditions which may be self-limited. It is hard to define a group with uniform severity, for its cardinal symptoms of cough and sputum may occur at almost any stage in the course of several chronic respiratory diseases.

By contrast, the identification of obstructive ventilatory disease requires only very simple tests, permitting a relatively homogenous group to be defined by objective methods. The hypothesis that obstructive disease is caused or aggravated by inhalation of polluted air is one which suggests effective preventive measures as a promising area for further studies. Finally, the collection under one rubric of cases with a common course, and possibly a common etiology, permits a fair appraisal of the importance of the condition compared with other diseases, thereby encouraging diagnosis, research, and education.

Fletcher (30) proposes the name of "chronic bronchitis" for "persistent or recurrent excessive mucous secretion in the bronchi." The natural history of the disorder is almost identical to that described above. He agrees that the term, "chronic obstructive disease of the lung" is a useful one to describe those cases with definite evidence of such obstruction, but he prefers to use it to describe a complication of bronchitis.

It may not seem of great importance whether the focus of attention is put upon chronic bronchitis and its complication, obstructive disease, or upon obstructive disease and its common precursor, chronic bronchitis. However, prevention of the morbid process through minimizing exposures to polluted air (including pollution with cigarette smoke) and individualized patient management, using repetitive measurement of function, could well be encouraged by focusing upon the presumably more serious condition, chronic obstructive disease.

Obstructive ventilatory disease of the lung could be compared to vascular hypertension; both are chronic, they are not invariably associated with pathologic changes, they each have a phase which is progressive and severely disabling. Each is based, essentially, on a dynamic measurement. Vascular hypertension is related to the pressure with which the heart ejects blood and the relationship of the vascular elasticity to that pressure. Ventilatory obstructive disease is related to the pressure within the chest which provides the gradient governing exchange with the external atmosphere; in the emphysematous type, elasticity is intimately related to the disease process. Each can be detected by fairly simple methods; neither implies a fixed etiologic basis for the disorder.

Although it is hoped that uniform criteria for diagnosis of this group of diseases may soon be decided upon, it may be premature to attempt

this now. Some criteria are suggested, but final decisions should be made by a group of persons with various qualifications and experience. It may be that entities which are homogenous and meaningful for epidemiologic purposes are not the ones which are most useful for clinical purposes.

In any event, the epidemiologic studies to be reported do attempt to group persons by symptoms, lung function tests, physical signs, and by exposure history.

No attempt will be made to apply a set of uniform diagnostic criteria for two reasons. First, diagnosis should be made in a clinical context; much of the work to be reported is made in the context of a survey or screening program. Second, a number of uncertainties remain about which uniform criteria should be used; for example, how to define dyspnea, which test to use, and what constitutes deviation from normal.

A series of studies has been undertaken with primary emphasis on methods for studying these conditions. These studies, which will be reported later, include: evaluation of criteria used by physicians in selecting causes of death; a pretest of an inquiry among the next of kin of persons dying from these causes concerning smoking and occupational and residence history of the deceased; methods for the study after a three-year period of a panel of persons with chronic respiratory symptoms; evaluation of pulmonary function tests for studying large population groups; methods for screening for obstructive disease among an employed group; methods for screening for obstructive disease among men in a chronic disease hospital; study of the effects of air pollution on a group of elderly males.

Summary

There has been a rapid increase in the number of deaths from pulmonary emphysema, together with a smaller increase in deaths due to the related diagnoses, asthma, bronchitis, bronchiectasis, and chronic interstitial pneumonia. Principles of nomenclature of these diseases have been reviewed. "Obstructive ventilatory disease of the lung" is suggested as a name for this group of disorders, and criteria for its use have been suggested. If the increasing frequency of these disorders is to be halted and the disease prevented, epidemiologic and clinical studies must be undertaken, using unequivocal criteria for symptoms and laboratory tests. The concept of obstructive ventilatory disease has some important advantages for this purpose when compared with the diagnoses of asthma, chronic bronchitis, or emphysema.

Sumario

Estudios Epidemiológicos de la Enfermedad Ventiladora Oclusiva del Pulmón: I. Repaso de los Conceptos y la Nomenclatura

Ha habido un rápido aumento en la mortalidad debida al enfisema pulmonar, junto con otro más pequeño en la debida a las enfermedades afines, asma, bronquitis, bronquiectasia y neumonía intersticial crónica. Se han repasado los principios que gobiernan la nomenclatura de estas dolencias. Para este grupo de trastornos se propone el nombre de "enfermedad ventiladora oclusiva del pulmón," exponiéndose las pautas que regirían su empleo. Si va a contenerse la creciente frecuencia de estos trastornos y a impedirse la enfermedad, hay que emprender estudios epidemiológicos y clínicos, usando pautas inequívocas para los síntomas y las pruebas de laboratorio. El concepto de enfermedad ventiladora oclusiva posee algunas ventajas importantes para dicho propósito cuando se compara con los diagnósticos de asma, bronquitis crónica o enfisema.

Resume

Etudes épidémiologiques de la maladie pulmonaire d'obstruction ventilatoire: I. Une revue des concepts et une nomenclature

Il y eut une augmentation rapide des morts par emphysème pulmonaire, en même temps qu'une augmentation moindre des morts dues à des diagnostics voisins, tels que de l'asthme, de la bronchite, des bronchiectasies, et des pneumonies interstitielles chroniques. Les auteurs ont revus les principes de la nomenclature de ces maladies. "La maladie obstructrice du poumon" est proposée comme nom du groupe de ces troubles, et les auteurs ont suggéré des critères pour son utilisation. Si la fréquence croissante de ces troubles doit être arrêtée et la maladie prévenue, des études épidémiologiques et cliniques doivent être entreprises, utilisant des critères non équivoques concernant les symptômes et les examens de laboratoire. Le concept de maladie d'obstruction ventilatoire a quelques avantages importants pour ce but là, quand on le compare avec les diagnostics d'asthme, de bronchite chronique ou d'emphysème.

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BULLOUS EMPHYSEMA[1]

A Long-Term Study of the Natural History and the Effects of Therapy

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Introduction

Numerous classifications of bullous emphysema have been offered, some based upon anatomic, others upon developmental or congenital, and still others upon clinical and physiologic, considerations (1–4). From observation of a group of patients with this disease over a period of ten years, the present writers believe that emphasis on physiologic abnormalities provides the most realistic approach to clinical problems, particularly those of therapy. Baldwin and associates (1) suggested that ventilatory insufficiency and the presence or absence of generalized emphysema are among the criteria which helped them decide the need for, and probable success of, excisional surgery. The present writers have approached this problem in a similar fashion but, in contrast to reported studies, they have had the opportunity to observe patients with this disease over a period of many years.

The purposes of this paper are: to describe some of the aspects of the natural history of bullous emphysema; to elucidate mechanisms of production of the disease by correlation of clinical and functional observation; and to examine the results of surgery and various modes of medical therapy.

Material and Methods

Observation of 15 male patients between the ages of twenty-three and forty-five are the basis of this report. These patients were selected initially on the basis of abnormal chest roentgenograms demonstrating one or more bullae occupying at least one quarter of the volume of one lung.

The clinical history obtained from each patient included details of smoking habits, cough, sputum, previous respiratory disease (including childhood infectious disease), and exposure to any unusual inhalants. On physical examination, particular attention was given to signs of bronchitis, pulmonary hypertension, and clubbing. During chest fluoroscopy, emphasis was placed on observations of air-trapping, mediastinal shift, herniation of bullae, and extent of diaphragmatic motion. Chest films were taken in inspiratory and expiratory phases. At intervals of six months to one year these observations were repeated in detail. In 12 of the 15 patients it was possible to collate and personally review military and industrial roentgenograms taken one to fifteen years prior to admission to this study. Routine studies on each patient included hemograms, electrocardiograms, and sputum cultures.

Pulmonary function studies were performed on each patient, utilizing standardized techniques previously reported (5–7). Measurements included lung volumes, maximal breathing capacity, ventilation at rest and with exercise, and detailed gas exchange studies. With the exception of one patient, these studies were serially repeated. In order to eliminate the variables of smoking and bronchial infection, pulmonary function studies were performed only after hospital observation and occasionally appropriate medical therapy. In patients treated surgically, repeat pulmonary function studies were delayed until complete recovery from all postoperative disability.

Venous angiocardiography, using the method of Robb and Steinberg (8), was performed on 8 patients, in some both preoperatively and postoperatively. Bronchograms were obtained on 4 patients; differential bronchospirometry, using the Carlens catheter, on 5 patients.

In addition to the 15 patients studied in detail, long-term clinical and roentgenographic observations were made by one of the writers (D. J. S.) on 15 unselected patients with large bullae in the 50- to 70-year age group. These two groups will be compared.

Observations

Background factors: Analysis of the histories of the 15 patients reveals no consistent pattern in regard to race, occupation, childhood disease, or previous acute respiratory diseases. Two patients, however, had pertussis in childhood (*Cases 4* and *15*), and one patient had been exposed to silica dusts (*Case 13*). The age range of twenty-three to forty-five years reflects a World War II veteran population age group and the method of selection used in the study.

Nine patients (*Cases 2, 4, 6, 7, 8, 10, 12, 13, 14*) smoked a minimum of 30 cigarettes daily for at least ten years prior to admission to this study; 3

[1] From the Chest Section and the Cardiopulmonary Laboratory of the Veterans Administration Hospital, Bronx, New York.

patients (*Cases 3, 5, 11*) smoked 10 to 30 cigarettes daily for a similar period; the remaining 3 patients (*Cases 1, 9, 15*) smoked irregularly or not at all.

Clinical observations (table 1): In 10 of the 15 cases the initial diagnosis of bullous emphysema was made on the basis of a routine chest roentgenogram taken for insurance or industrial purposes or as part of a study of nonpulmonary illnesses. In one patient (*Case 7*) the diagnosis was made at the time of a spontaneous pneumothorax. The other 4 patients sought medical attention because of symptoms of bronchitis (cough, bronchorrhea, intermittent wheezing, and dyspnea). It should be noted, however, that in all but 3 of the patients in whom the diagnosis had been made on a chance chest roentgenogram, there was evidence early in the study of symptoms or signs of bronchitis. In all of the patients with these symptoms, physical signs of wheezing, rhonchi, or coarsening of breath sounds were noted at some time in the course of the disease, especially during the exacerbations associated with superimposed respiratory infection. This complex of symptoms and physical signs will be alluded to by the term "symptomatic bronchitis."

In addition to the physical signs of bronchitis, the usual signs described in the presence of large bullae were noted, i.e., hyperresonance and diminished or absent breath sounds. In 3 patients (*Cases 7, 8, 13*) signs of generalized emphysema were noted, consisting of diminished breath sounds and prolonged expiration over areas of the lung not grossly involved by bullae. This was in contrast to the remainder of the patients in whom breath sounds were normal in those areas. Rales were present over both lower lobes in one patient with proved bronchiectasis, the only patient in the series with this diagnosis. In no case were clubbed fingers or an accentuated second pulmonic heart sound noted.

Roentgenographic and fluoroscopic observations: At the time of admission to this study, the extent of bullous disease ranged from one quarter of the roentgenographic volume of one lung to three quarters of the total volume of both lungs. In all but one case (*Case 6*), the bullae were predominantly in the upper lung fields, and in this case the bulla which appeared to be located in the right lower lung field was found to arise from the right upper lobe at the time of surgery. In the other patients who underwent one or more surgical procedures, the roentgenographically prominent bullae were found to arise from upper lobes.

Various manifestations of air-trapping were noted in each patient. The most common finding was increased radiolucency and increase in bulla size during forced expiration. This was usually accompanied by severe limitation of diaphragmatic motion on the affected side. In those patients in whom mediastinal herniation occurred, the function of the contralateral diaphragm was also impaired. Mediastinal shift with forced expiration could be demonstrated in 12 patients, in 5 of whom herniation of a large bulla to the opposite side was noted. It was significant that repeated observations of the same patients over a period of years revealed considerable variation in the degree of air-trapping, mediastinal shift, and diaphragmatic motion. This phenomenon could not be correlated with the presence or absence of symptoms, or with signs of bronchitis. As will be described below, certain changes in pulmonary function could be related to the variations in air-trapping noted fluoroscopically and roentgenographically.

The period of retrospective observation of chest films averaged eight years (range three to fifteen years) in the 12 patients in whom it was possible to obtain such information. In this group normal initial chest films were found in 4 patients. In these 4 patients serial roentgenograms revealed the gradual appearance and progressive enlargement of one or more bullae. In 7 of the remaining 8 patients, the earliest available films revealed small apical bullae at the sites eventually occupied by large bullae. In the other case (*Case 3*), the pattern of almost complete bullous involvement of the left side was not recognized on the original army films three years prior to admission because of the remarkably homogeneous loss of normal "markings" on the affected side (figure 1). In this patient, roentgenograms were unchanged through eight years of follow-up observation. In the 3 patients in whom no previous chest films were available, the observation period was too short to permit a statement as to the progress of bullous changes. Although it is clear that in this series the great majority of these bullae progressively enlarged, it is apparent from the observations that there was no uniformity as to the rate of progression. In addition, there was no correlation between symptoms and

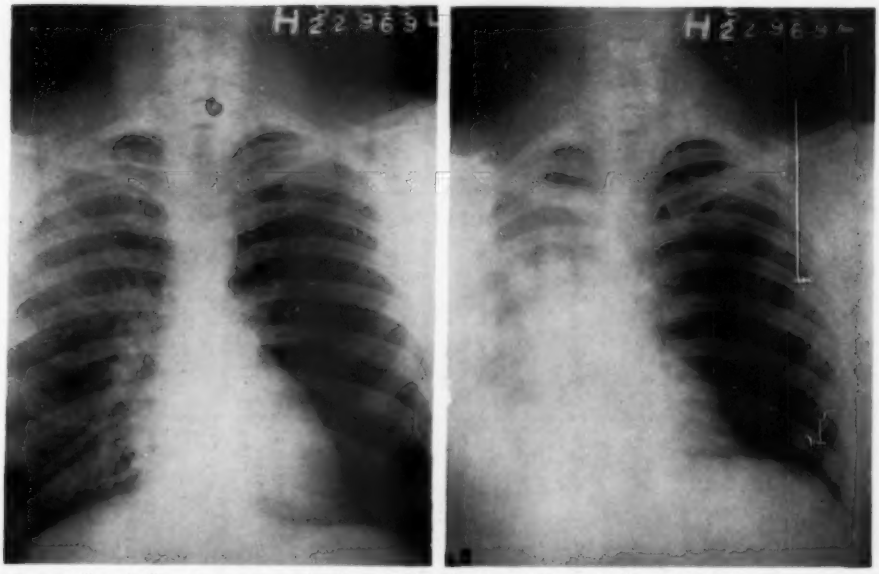

FIG. 1. *Case 3.* Roentgenogram showing (*A*) inspiration; (*B*) expiration. Marked air-trapping and mediastinal shift are shown.

either size or rate of enlargement of bullae. This was most striking in the 3 patients in whom symptomatic bronchitis was absent or minimal and in whom bullae progressed rapidly.

Miscellaneous observations: The 12 lead electrocardiograms were normal on all patients. There was, specifically, no evidence of right ventricular hypertrophy or strain pattern over the average follow-up period of five years. This correlates well with observations of normal pulmonary arterial pressure at rest and exercise in 3 patients (in this group) who had cardiac catheterization (9).

The bronchial tree was studied in 5 patients by bronchoscopy, bronchography, or both. In no case was a congenital anomaly of the bronchial tree found. In *Case 3*, with bullous involvement of an entire hemithorax, these studies demonstrated the presence of a bronchial tree of diminished caliber on the affected side. The combination of detailed fluoroscopic, angiocardiographic, and bronchial anatomic studies in this case was believed to be conclusive evidence in support of the diagnosis of bullous emphysema, and against an alternative diagnosis of pulmonary agenesis. Pulmonary function studies confirmed this viewpoint.

Analysis of Pulmonary Function Studies

(Tables 2 and 3)

It is apparent that generalization as to representative or mean values cannot be made. Serial studies of lung volumes reveal considerable variation in residual volume, independent, in most cases, of similar variations in vital capacity and maximal breathing capacity. This is seen in the comparison of different cases as well as in serial studies of the same patient, and is well illustrated in *Case 3*, in which profound changes in residual volume over a period of five years are accompanied by minimal changes in vital capacity and maximal breathing capacity. This apparent discrepancy in residual volume and other parameters of ventilatory function has been noted previously and is related to the imperfect ventilation of isolated bullae (1). Similarly, the alveolar nitrogen value determined by the open-circuit method for residual volume, while usually abnormal in this series, reveals considerable variation in the same patient and is independent of changes in residual volume. This variation is partially a reflection of the crudeness of the technique as well as a reflection of changing degrees of bulla ventilation.

TABLE 1

CLINICAL SUMMARY*

Patient	Age on Admission	Symptomatic Bronchitis	Bulla Size and Location	Prior Roentgenograms	Surgery	Clinical Course	Roentgenographic Course
1	29 (1953)	Absent	Upper one-half left; upper one - third right	1943–1946, small right apical bulla	None	4 years—asymptomatic	Entire left and one half right lung involved
2	23 (1952)	Severe	Upper one - fourth left; upper one-half right	1947, small right apical bulla	None	5 years — progressive bronchitis	Slight bulla enlargement
3	25 (1953)	Slight	Entire left lung	1950, similar	None	6 years—asymptomatic	Unchanged
4	31 (1957)	Moderate	Upper one-half bilateral	1954, small bilateral bulla	None	2 years—asymptomatic	Unchanged
5	44 (1956)	Absent	Upper one-half left	1942, normal; 1950–1956, progression of bulla and closure of right-sided bulla following tuberculosis	None	2 years—unchanged	Unchanged
6	44 (1952)	Moderate	Lower one - third right; and small bulla, upper right	None	1952, bullectomy	1 year—asymptomatic	Roentgenographic stability
7	29 (1953)	Severe	Upper one-half bilateral	None	Right upper lobectomy, 1953	Progressive generalized emphysema after a 3-year remission	Stable
8	34 (1949)	Moderate	Upper one-third bilateral	1940, normal; 1943, apical bullae	Bilateral bullectomy 1950	10 years—slow progression	Numerous small bullae developed
9	34 (1954)	Absent	90 per cent right upper; one-third left	1947, small bilateral bulla	Bilateral bullectomy 1954–1955	5 years—asymptomatic	Stable
10	33 (1953)	Mild	Upper two - thirds left; right apical	None	1953, left upper lobe lobectomy	6 years—slight progression of bronchitis	Stable on left; enlarging bulla on right
11	23 (1950)	Mild	Entire left side; right apex	1941, normal; 1945, small left-sided bulla	Left upper lobe bullectomy	8 years—asymptomatic	Stable
12	45 (1954)	Moderate	Upper one-half, bilateral	1943, normal; 1945, apical bulla	Multiple bullectomy, bilateral upper lobes	5 years—asymptomatic	Stable
13	42 (1950)	Moderate	Entire right lung; one - fourth left lung	1942, bilateral small bulla; 1945, upper one-half right lung; one-fourth of left lung	Bullectomy, right upper lobe	1 year — unchanging bronchitis	Stable
14	33 (1950)	Mild	Upper one-third left lung; upper one-fourth right lung	1943, apical bullae bilateral; 1945, progressive; 1955, entire left one-half right lung	Left upper lobe bullectomy	4 years—asymptomatic	Stable, right-sided bullae
15	25 (1951)	Moderate	Two-thirds right upper multiple, small on left	1942, one-third right lung; 1946, two-thirds of right lung and left lower	Multiple bullectomy and thoracoplasty, right side	7 years—remission of symptoms	Roentgenographic stability

* More complete clinical details on these patients are given in the appendix table attached to the reprint of this paper.

TABLE 2

LUNG VOLUMES AND VENTILATION

Case	Lung Volumes* (per cent of predicted)			RV/TLC × 100	$F_{A_{N_2}}$†	MBC (per cent of predicted)	$\dot{V}_{E/m^2}$‡		
	VC	RV	TLC				Basal	Exercise	First Minute Recovery
Normal	100	100	100	<30	<2.5	100	<4.0	<10.0	<12.0
1 (a) 8/26/53	65	109	74	29	4.7	93	5.9	8.6	14.1
(b) 8/21/57	35	142	60	48	8.9	51	4.7	12.6	18.3
2 (a) 11/21/52	100	177	110	32	10.0	103	4.7	10.3	14.6
(b) 12/7/53	93	180	109	33	9.2	94	4.1	9.4	15.3
(c) 9/13/55	85	104	94	22	6.7	81	4.0	10.0	16.6
3 (a) 4/28/53	66	146	96	31	3.8	71	5.1	11.0	17.0
(b) 5/17/55	66	66	66	20	4.1	78	3.7	7.7	13.2
(c) 11/14/56	70	136	83	33	7.2	89	3.4	10.3	12.9
(d) 3/17/58	79	168	109	30	9.1	81	3.8	8.7	11.2
4 (a) 2/8/57	89	145	102	27	1.7	74	5.2	12.0	
(b) 9/17/57	96	75	91	16	1.7	87	4.8	12.7	18.7
(c) 3/23/59	97	132	107	25	2.4	80	4.5	12.6	18.2
5 (a) 5/20/57	76	180	112	39	3.9	65	4.1	11.1	
(b) 7/19/57	100	184	119	38	8.0	74	3.7	10.4	11.7
6 (a) 9/3/52 preoperatively	53	92	69	33	8.9	54	5.7	16.2	20.8
(b) 4/22/53, 7 months postoperatively	65	135	86	38	4.0	67	5.1	12.7	18.6
7 (a) 5/27/53 preoperatively	55	410	115	70	8.8	26	5.5	10.6	14.9
8 (a) 5/17/49 preoperatively	79	165	97	34	—	73	4.7	11.7	
(b) 7/24/50 postoperatively	59	107	72	35	1.9	88	4.0		
(c) 8/4/53	75	201	107	46	—	51	4.6	10.2	11.2
(d) 4/12/56	65	153	88	43	4.6	47	5.3	10.6	15.8
(e) 11/5/57	71	174	98	44	5.0	68	4.2	8.2	13.3
(f) 1/16/58	73	192	103	46	4.1	72	4.5	12.5	13.3
9 (a) 10/18/54 preoperatively	105	208	134	33	8.2	63	3.6	9.5	16.0
(b) 5/12/55 postoperatively; right	109	152	119	25	3.7	109	3.6	10.4	13.0
(c) 7/19/56 postoperatively, bilateral	115	108	114	23	3.4	125	3.5	7.6	10.8
(d) 8/5/57	121	116	119	24	3.4	106	3.3	7.5	11.6
10 (a) 3/13/53	92	159	109	29	5.5	88	4.5	11.9	14.2
(b) 7/6/55, 2 years postoperatively	90	140	100	28	3.3	80	4.4	13.7	23.2
(c) 5/12/58	110	117	112	23	2.3	86	4.5	12.5	20.8
11 (a) 1/3/51 preoperatively	62	97	75	26	2.3	67	4.8	11.5	18.1
(b) 5/7/51 postoperatively	73	160	92	35	1.8	95	3.6	10.0	12.5
(c) 7/16/53	83	151	95	31	3.4	99	4.2	6.2	10.2
(d) 6/14/55	92	162	111	35	2.8	100	4.0	7.9	12.3
(e) 6/3/57	91	123	102	29	2.1	88	3.4	9.3	8.6

TABLE 2—*Concluded*

Case	Lung Volumes* (*per cent of predicted*)			RV/TLC × 100	$F_{A_{N_2}}$†	MBC (*per cent of predicted*)	$\dot{V}_E/m^2$‡		
	VC	RV	TLC				Basal	Exercise	First Minute Recovery
12 (a) 6/9/54 preoperatively	66	260	121	51	4.5	59	3.7	6.8	13.3
(b) 1/12/55 postoperatively	93	203	120	41	1.5	91	3.4	7.6	10.5
(c) 6/20/55	93	103	100	24	2.7	95	4.1	7.4	13.5
(d) 5/27/57	91	106	95	23	4.6	75	6.9	10.0	13.6
13 (a) 9/21/50 preoperatively	54	138	90	39	3.6	52	5.2	16.1	18.0
(b) 1/24/51 postoperatively	66	147	78	33	3.6	61	5.2	13.2	17.2
14 (a) 10/5/50	93	121	99	24	3.5	62	—	—	—
(b) 7/20/55 preoperatively	66	97	78	31	4.3	40	3.8	11.7	13.0
(c) 7/22/57 postoperatively	104	131	115	29	5.7	69	3.7	11.0	13.6
15 (a) 11/6/46	98	276	133	44	—	48	6.4	14.1	—
(b) 3/14/51 preoperatively	92	184	118	31	4.5	68	4.7	12.2	13.4
(c) 7/3/58, 7 years postoperatively	103	127	110	27		50			

* VC—vital capacity
RV—residual volume
TLC—total lung capacity
† $F_{A_{N_2}}$—Per cent nitrogen after seven-minute oxygen breathing
‡ $\dot{V}_E/m^2$—volume of expired gas (total ventilation per square meter of body surface area)

Except for isolated instances, clear-cut reductions in vital capacity were associated with similar reductions in maximal breathing capacity and, therefore, it is useful to use these as indices of ventilatory insufficiency. The initial studies in at least 13 of the 15 patients showed evidence of such ventilatory insufficiency.

Spirograms in all 15 patients failed to disclose significant air-trapping, and this was true even in patients with severe bronchitis and marked reduction of maximal breathing capacity. This inability of the spirogram to reflect obstruction is well known. It is of interest to note that fluoroscopic observations in many patients clearly showed bronchial obstruction and air-trapping which was not seen in ordinary or differential spirometry. In an effort to understand some of these mechanical factors, a study of lung compliance and resistance has been recently undertaken in this laboratory.

Analysis of the standard exercise oxygen consumption tests revealed no consistent pattern. Variation in the same patient, unrelated to clinical or other functional changes, is well illustrated by *Case 11*. The wide range of the exercise oxygen consumption results has been known for many years and is explained by the fact that the 30-step exercise test is not quantitative in terms of physical work. With this particular test, unless values are below 350 cc. per min. per m^2, no physiologic significance in terms of reduced blood flow can be deduced. In the present group, there was no individual patient in whom the exercise oxygen consumption had significance, with the possible exception of the abnormally low value in the patient of *Case 7* who subsequently developed decompensated cor pulmonale.

Gas exchange was evaluated by analysis of the measurements of rest and exercise arterial oxygen saturation, the determination of alveolar-arterial oxygen gradients at rest at two levels of inspired oxygen, and the carbon dioxide tensions. At

TABLE 3

Oxygen Consumption and Gas Exchange

Case	$\dot{V}_{O_2}$*/m²		Sa_{O_2}†			Room Air					Low Oxygen				
	Basal	Exercise	Basal	Exercise	Low O_2	Pa_{CO_2}‡	PA_{O_2}§	Pa_{O_2}‖	A-a Gradient	$\dot{V}_D$¶ (% of V_T)	Pa_{CO_2}	PA_{O_2}	Pa_{O_2}	A-a Gradient	V_D (% of V_T)
						mm. Hg					*mm. Hg*				
Normal	129 ± 13 cc.	480 ± 74 cc.	96 ± 2%	96 ± 2%		40	100	90–100	<12	<30	40	—	—	<12	<30
1 (a)	134	410	97.5		92.0	32	113	97	16	31	33	75	72	3	34
	132	332	97.5	87.2	76.0	30	113	92	21	20	26	80	72	8	19
2 (a)	158	404	91.1	87.7	82.1	45	96	67	29	37	40	62	47	15	34
(b)	136	381	95.5	87.7	83.8	36	105	79	26	20	32	73	58	15	21
(c)	135	362	94.1	90.3	85.5	30	111	66	45	15	30	72	46	26	18
3 (a)	150	633	99.4	95.4	92.0	34	110	102	8	21	33	72	66	6	16
(b)	142	422	96.5	95.6	88.3	41	101	92	9	21	33	63	52	11	14
(c)	134	454	99.0	95.4	89.0	35	107	87	20	12	34	70	55	15	14
(d)	147	441	93.7	97.6	87.6	35	108	97	11	11	44	61	57	4	28
4 (a)	146	471	92.5	91.5	86.5	38	105	83	22	36	33	72	52	20	30
(b)	139	495	94.5	95.0	88.7	29	118	93	25	14	29	79	61	18	16
(c)	152	500	94.4	90.7	87.0	35	111	75	36	15	33	70	52	18	16
5 (a)	138	412	93.5	92.9	83.5	30	113	85	28	9	29	74	55	19	18
(b)	120	325	93.4	91.4	87.9	29	108	88	20	21	29	81	73	8	19
6 (a)	131	472	94.0	86.6	87.7	35	109	88	21	38	34	74	65	9	40
(b)	129	460	96.7	95.1	86.5	36	105	84	21	37	38	64	63	1	40
7 (a)	142	298	96.3	85.8	85.7	42	98	81	17	46	35	73	58	15	39
8 (a)	127	425	92.0	93.0	82.0	38	108	79	29	30	33	53	45	8	29
(b)	115	—	96.8	—	81.4	38	104	92	12	25	42	39	38	1	14
(c)	136	364	90.0	92.5	85.7	42	97	74	23	40	35	71	47	24	39
(d)	139	390	84.5	88.4	82.7	38	107	69	38	29	35	69	57	12	31
(e)	107	302	91.4	88.0	85.6	34	107	74	33	37	36	68	55	13	64
(f)	121	408	88.0	95.0	86.0	34	108	84	24	29	33	68	66	2	29
9 (a)	124	357	94.6	90.5	85.5	35	109	90	19	18	39	64	59	5	31
(b)	117	464	95.8	94.5	87.3	35	110	92	18	20	34	67	46	21	20
(c)	128	335	93.8	91.5	87.5	35	105	101	4	19	33	66	51	15	17
(d)	121	439	93.7	92.7	86.0	34	107	98	9	20	37	61	61	0	24
10 (a)	157	582	95.8	93.5	91.3	32	108	86	22	17	40	77	69	8	19
(b)	170	567	97.6	91.5	87.6	31	97	94	3	29	37	60	59	1	32
(c)	175	510	92.0	87.5	87.0	32	109	85	24	11	33	75	56	19	19
11 (a)	145	417	96.5	94.7	—	42	97	95	2	35	—	—	—	—	—
(b)	140	466	97.4	97.0	—	45	96	89	7	25	—	—	—	—	—
(c)	130	286	94.4	90.4	86.0	46	95	88	7	38	49	55	74	19	41
(d)	128	385	96.9	90.0	84.8	34	107	90	17	18	31	64	48	16	16
(e)	148	497	92.0	93.5	81.0	36	101	85	16	29	41	56	69	13	30
12 (a)	140	315	92.0	91.4	86.4	50	93	75	18	35	46	64	55	9	48
(b)	139	348	95.6	94.0	92.1	34	108	96	12	3	34	70	72	−2	10
(c)	144	325	96.5	94.0	93.5	42	103	92	11	27	38	73	65	8	23
(d)	232	399	98.8	96.4	97.5	35	106	102	4	27	32	73	72	1	11
13 (a)	161	461	89.4	83.8	—	60	77	71	6	55	—	—	—	—	—
(b)	162	455	90.6	85.5	—	47	94	68	26	38	—	—	—	—	—
14 (a)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
(b)	107	—	94.0	89.3	87.4	35	111	89	22	22	31	69	56	13	18
(c)	115	457	92.1	98.5	82.9	29	108	95	13	22	31	63	58	5	24
15 (a)	156	488	97.9	92.1	—	—	—	—	—	—	—	—	—	—	—
(b)	142	375	95.5	85.4	73.3	43	97	93	4	28	41	47	40	7	33
(c)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

* $\dot{V}_{O_2}$—oxygen consumption
† Sa_{O_2}—saturation with oxygen
‡ Pa_{CO_2}—partial pressure of carbon dioxide in arterial blood
§ PA_{O_2}—alveolar oxygen pressure
‖ Pa_{O_2}—partial pressure of oxygen in arterial blood
¶ V_D—volume of dead space gas, V_T—tidal volume

some time during the course of the study, 14 of the 15 patients (except *Case 3*) had exercise oxygen saturation values below 92 per cent, but in none was this below 84 per cent. Analysis of alveolar-arterial oxygen gradients at rest revealed gross abnormalities, i.e., a gradient above 20 mm. of mercury, in approximately half of these cases. It is to be presumed that, with a steady-state exercise, abnormal gradients would have been present in all patients with exercise unsaturation. The data reveal that the gradient abnormalities are explicable entirely on the basis of increased venous admixture. In no case was there clear-cut evidence of impairment of diffusion.

No consistent relationship between gas exchange and ventilatory abnormalities was noted. For example, *Cases 1*, *6*, *7*, and *13* had the most marked evidence of ventilatory insufficiency, and all had low arterial oxygen saturation values in the range of 84 to 87 per cent with exercise. There were, however, several patients with similar levels of abnormal arterial oxygen unsaturation in whom the ventilatory function was relatively normal (*Case 2* and *Cases 10c* and *15b*).

Differential bronchospirometry revealed significant reduction in the oxygen consumption of the involved lung in patients with unilateral bullae (*Cases 3*, *10*, *11*, *15*). In 2 of these patients (*Cases 11* and *15*), the ventilation partition was almost normal and, in the other 2, the reduction in ventilation on the affected side paralleled the reduction in oxygen consumption. In one patient (*Case 2*) with bilateral bullae, fairly normal partition of ventilation and oxygen consumption was observed. In *Case 11*, postoperative bronchospirometry revealed a return to normal ventilation and oxygen consumption partition. This is of interest because postoperative angiocardiograms (figure 2) revealed a return to grossly normal circulation on the operative side in this patient as well as in the other patient (*Case 6*) in whom a postoperative angiocardiogram was performed. In all patients in whom both differential bronchospirometry and angiocardiography were done, there was excellent correlation between the lack of vascularization and the reduction in oxygen consumption on the side containing the major bullae.

Several mechanisms may account for the basic gas exchange abnormality. It is apparent that large bullae do not receive significant amounts of pulmonary arterial circulation and presumably are "nourished" by the systemic circulation. In view of stated observations which indicate vary-

FIG. 2. *Case 11*. Angiocardiograms: (*A*) preoperative; (*B*) postoperative.

ing degrees of ventilation to the bullae, it is reasonable to view such bullae as functionally dynamic dead spaces. It is unlikely that this dead space phenomenon can so decrease total effective alveolar ventilation to account for the observed arterial hypoxia. It has been demonstrated that the pulmonary arterial bed in areas adjacent to large bullae is compressed and distorted, and presumably alveolar ventilation is markedly impaired in these areas, thus leading to variable degrees of venous admixture. The prompt improvement of gas exchange in some of the patients who have been operated upon would tend to confirm this. Ineffective alveolar ventilation occurring in areas of lung other than those adjacent to bullae must also occur in some of the patients, particularly those in whom generalized bronchial disease is present. It is likely that the latter mechanism becomes most important as evidence of generalized emphysema develops. In some patients the relative importance of these two mechanisms cannot be determined readily without long-term observations.

Approximately two-thirds of the patients consistently responded to exercise with significant hyperventilation. The reason for this cannot be completely elucidated by analysis of the data. Although diminished arterial oxygen concentration with exercise may be a factor, the data reveal no specific correlation. Abnormal stretch reflexes arising in the area of overdistended lung or limitation of complete inspiration by increased pressure within the bullae may account for the hyperventilation. This suggests active participation by the respiratory center in this mechanism. In addition to the observed exercise hyperventilation, there appears to be some degree of resting hyperventilation, reflected by low arterial carbon dioxide tensions. As noted previously, these abnormalities cannot be explained on the basis of diffusion barriers.

Results of Therapy

The fundamental problem in assessing results of any therapy in patients with bullous emphysema is that of differentiating those symptoms, signs, and functional abnormalities due to generalized bronchitis from those due to bullae per se. This problem has been appreciated by some writers (1, 4), but is unfortunately overlooked in many studies. It is apparent from the analysis of the present clinical and functional material that the number of variables and their interrelationships preclude any quantitative appraisal of the results of therapy.

The high incidence of symptomatic bronchitis in these patients has been alluded to previously. In most, it has been possible to produce at least temporary improvement in the bronchitis by means of medical therapy that included bronchodilators, antimicrobials, and cessation of smoking under hospital observations. Unfortunately, most of the study group did not consistently follow this regimen after discharge from the hospital so that the effect of long-term medical therapy on the course of the disease cannot be fully evaluated.

Ten patients had one or more surgical procedures performed. The decision to perform surgery was not made on the basis of randomization, because of the relatively small number of patients available and the variability of the clinical and functional data as noted above. Surgery was recommended to all patients in whom there was evidence of either extensive bullous disease or evidence of progression. Three of the patients met these criteria (*Cases 1*, *3*, and *4*) but refused surgery.

Resection of single or multiple bullae was performed in each case. In 2 patients early in the series, catheter drainage of the largest bulla was attempted as a preliminary procedure prior to resection. This was done to evaluate the degree of expansion of lung compressed by bullae. As it became obvious that postoperative lung expansion presented no problem, this procedure was abandoned in favor of removal of large bullae and ligation of smaller ones. In only one patient (*Case 7*) was it necessary to remove an entire lobe. Two patients had small thoracoplasties and 2 others had pleural-tent procedures performed. These procedures were deemed necessary by the surgeon because of the fear that underlying compressed lung would not expand or that overdistention of possibly emphysematous lung might occur. Again, with experience these operative techniques proved to be unnecessary and were abandoned. An insignificant infection of the pleural space occurred in one patient (*Case 10*).

Adequate postoperative follow-up observation of at least four years is available in all but 2 patients (*Cases 6* and *13*). Of the remaining 8 patients, 2 (*Cases 7* and *8*), as noted above, had physical findings and functional evidence of

generalized emphysema. Postoperatively, the patient of *Case 7* had a three-year remission in symptoms, following which pulmonary insufficiency progressed rapidly to decompensated cor pulmonale. This case illustrates some of the pitfalls in interpreting therapeutic results. It is tempting to assume that the three-year postoperative remission was due entirely to surgery, but it is clear that remission had occurred prior to operation and that this could be related in some fashion to medical therapy and cessation of smoking. It is interesting to note that the postoperative remission ended at a time when the patient resumed heavy smoking. Eight years of postoperative follow-up in *Case 8* revealed no significant change from the preoperative clinical or functional state. In view of this, it is impossible to assess completely the role of surgery. One might speculate that surgery was beneficial in that it delayed progression of the disease. On the other hand, the patient maintained himself on a good medical regimen during the postoperative period, i.e. bronchodilators, a minimal amount of smoking, and treatment of exacerbations of bronchitis, and it seems likely that this is responsible for the stable course. In contrast to patients with only localized bullous disease, this patient never demonstrated improvement in ventilatory function after operation.

Case 10 illustrates the type of patient in whom bullectomy does not alter the clinical course of symptomatic bronchitis. In addition, function studies revealed no change in ventilatory function and, if anything, a worsening of gas exchange characterized by a decrease in arterial oxygen saturation with exercise. In view of the observation of *Cases 7* and *8* discussed above, it would be of interest to follow this patient's course over a period of years to see if generalized emphysema ensues.

The remaining 5 patients (*Cases 9, 11, 12, 14, 15*) demonstrated clear-cut improvement following surgery. This included disappearance of symptoms and significant improvement in ventilatory function. In 2 of the patients, exercise hyperventilation, present preoperatively, was no longer apparent. *Case 14* was observed at frequent intervals over a period of five years before the patient consented to surgery. During this period the bullae were noted to enlarge rapidly, and symptomatic bronchitis progressed. Worsening of ventilatory function paralleled the clinical course. Following bullectomy, sumptoms disappeared completely, ventilatory function improved, and exercise arterial oxygen saturation became normal. The minimal gas exchange abnormalities in the other 4 patients in this group were not consistently altered by surgery. Four of the 5 patients in this group stopped smoking at the time of surgery. This and other factors previously discussed may have contributed to the observed improvement.

Each surgically treated patient developed a fixed mediastinum. This was accompanied by fluoroscopic evidence of significant improvement in diaphragmatic motion and marked diminution of air-trapping. In no case did herniation of bullae recur postoperatively. This evidence of mechanical improvement correlates well with the observed improvement of ventilatory function. Significant enlargement of remaining bullae postoperatively occurred in only 2 patients (*Cases 10, 14*). In view of the fixation of the mediastinum and probable pleural symphysis, this is not an unexpected observation. It suggests that, although surgery cannot completely eradicate bullous disease, it can restrict the potential space for progression of bullae. Thus, it is possible that simple mechanical or chemical pleurodesis may accomplish the same result.

Discussion

It seems clear that the basic abnormality in bullous emphysema is an imperfect bronchiolar communication which permits air-trapping and overdistention of isolated areas of pulmonary parenchyma. The most striking evidence for the existence of this communication is the demonstration histologically of bronchioles entering bullae in all resected specimens. That these bronchial communications are functional is borne out by the roentgenographic and physiologic observations previously cited. Among these are progressive enlargement of bullae, failure of bullae to close spontaneously, the elevated residual volumes, and normal partitions of ventilation with bronchospirometry in some cases. Furthermore, it is obvious that the bronchiolar-bulla communications are imperfect as evidenced by air-trapping during expiration. The increased intrathoracic pressure occurring in active expiration tends to collapse noncartilaginous bronchioles, resulting in a "check-valve" trap mechanism. The failure, despite repeated efforts, to introduce any radiopaque dye into these bullae is further evidence that the bronchiolar communi-

cation is abnormal. Some support for the thesis of imperfect bulla communication is offered by analysis of the histologic material. All sections revealed infiltration of bronchiolar walls with chronic inflammatory cells. In addition, inflammatory changes consisting of denudation of bronchial epithelium or, frequently, squamous metaplasia, were noted and were especially marked in the most distal portions of the bronchioles. In one specimen, the bronchiolar walls were surrounded by a cuff of inflammatory cells and areas of peribronchiolar fibrosis somewhat similar to that reported by Spain and Amberson, and others (11, 12). In retrospect, it seems likely that a better understanding of the bronchial communication would have resulted if the surgical specimens had been fixed in an inflated state. It is the writers' opinion that it is not necessary to demonstrate actual organic endobronchial obstruction to verify the thesis of imperfect communication between bullae and the bronchial tree. The inflammatory changes noted above, possibly accompanied by some edema in the intact specimen, could certainly diminish the caliber of passages of the diameter of third-order bronchioles. It could be expected that any process which completely obliterates the bulla communication with the bronchial tree would lead to bulla closure. This assumes that the only ingress of inspired air is through the bronchial tree and, furthermore, that there is sufficient vascular bed within the bulla to permit absorption of the trapped air. Clinical observations made by the present writers and others of the fate of the bulla following infection supports this hypothesis (13, 14). In one case in the present series (*Case 5*), as well as in 4 other cases observed by one of the writers (D. J. S.), bulla closure was noted very gradually over a period of several weeks after a bacterial infection within the bulla. The air-fluid level noted in figure 3 characterized all cases. Because of the large bulla size, it is unlikely that inflammatory induced granulation tissue could effectively cause approximation of the bulla walls and closure in that manner. Therefore, it is likely that inflammation due to infection completes the stenosis of the bronchial communication to the bulla.

It is obvious that multiple etiologic factors might play a role in either the development or function of the imperfect bronchial communication. That the bullae are not congenital cysts is clear from the evidence cited previously as well as from histologic study of the bulla linings. In no case was a secretory epithelial lining found. The bullae in this series were lined by simple fibrous tissue, although in some sections patches of respiratory epithelium were noted within the walls or actually contiguous with the lining of the connecting bronchiole. These changes can be interpreted as no more than feeble attempts at epithelization similar to that observed in some "healed" tuberculous or abscess cavities. Although it cannot be disproved that a congenital abnormality of bronchiolar epithelium may exist, it seems clear that this, in itself, is insufficient without some superimposed inflammatory process. The most likely cause of this inflammation is infection. It has been recognized that bullous-like structures develop during the course of acute necrotizing pneumonia or bronchiolitis during infancy and early childhood. The pathologic evidence in these cases, while not conclusive, suggests that these structures are not cavities resulting from necrosis of parenchyma, but are actually bullae (2). Similarly, this phenomenon has been observed in adults with diffuse organizing fibrosis of the lung. Even with these concepts in mind, careful evaluation of the clinical histories of the patients rarely revealed an instance of an isolated acute infection. It must be recognized, however, that the history of childhood respiratory infection is often unreliable. In this series, therefore, chronic and recurrent bronchitis has been the most likely cause of inflammation sufficient to initiate or aggravate the mechanisms previously described leading to bullous emphysema in certain patients. In addition to infection, cigarette smoking seems to be a factor in the progression of bronchitis. Considering the high incidence of chronic bronchitis, the apparent infrequency of giant bullous emphysema is not satisfactorily explained. For this reason as well as the lack of availability of detailed pathologic studies, it is impossible at this time to test further the hypothetical relationships of bullous emphysema and bronchitis.

The relationships between chronic bronchitis and generalized obstructive emphysema are more convincing. The clinical study of the 15 patients in the age group above fifty, previously cited, was based on the findings of bullae of magnitude similar to those in the younger age group. It can be categorically stated that all of these patients had typical symptoms and signs of generalized emphysema. Furthermore, they all

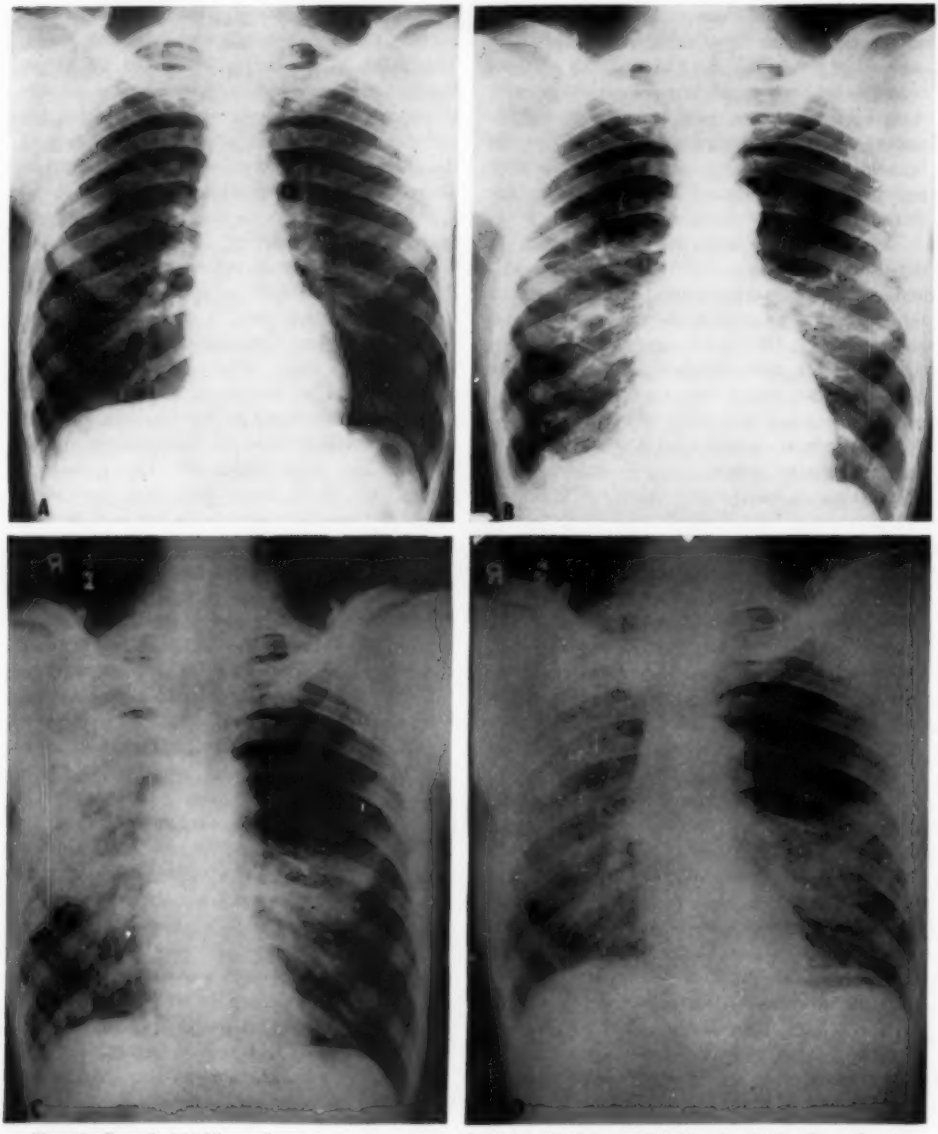

FIG. 3. *Case 5.* (*A*) Normal army roentgenogram in 1942; (*B*) bilateral bullae in 1954; (*C*) active tuberculosis of right lung with fluid level in bulla in February, 1956; (*D*) closure of right upper lobe bulla during therapy for tuberculosis in August, 1956.

had significant chronic, symptomatic bronchitis with frequent acute exacerbations and all had clinically significant pulmonary insufficiency, some with decompensated cor pulmonale. In contradistinction to the younger age group, the present observations led to the conclusion that the bullae in this group are not clinically significant. Roentgenographic observations over an

average four year-period did not demonstrate change in either size or shape of these bullae. Localized air-trapping phenomena could not readily be demonstrated. In the 4 patients in whom gradual closure of a large bulla was noted following infection, there was no improvement in symptomatology or function. This was true despite the expansion of compressed lung. The location of bullae in this group roentgenographically differed significantly from the location in younger patients in that the lower lung fields as well as the upper contained large bullae. Lacking pathologic proof, one may only speculate that most of these bullae arise from the upper lobes. Perhaps the fixation of the chest cage and mediastinum which occurs in these older patients accounts for the displacement of the bullae toward the less rigid diaphragmatic surface of the lung. It certainly can explain the absence of herniation and other manifestations of air-trapping. It would seem logical to assume that these giant bullae must have begun their "growth" at an earlier time, when the chest cage and mediastinum were mobile. From these observations and the almost universal occurrence of bronchitis in these patients, it might be speculated that the ultimate fate of many of the younger patients with bullous emphysema is the developement of generalized emphysema.

The results of therapy in the present group of patients, together with the hypothesis regarding pathogenesis, lead to several conclusions regarding the therapy of bullous emphysema. Although in any individual patient a generalization might not apply, it is nevertheless the belief of the present writers that the only common denominator to be used in approaching a decision for surgery is the demonstration of abnormal air-trapping mechanisms, leading to various degrees of ventilatory insufficiency, hyperventilation, and presumably an increase in respiratory work. Therefore, ideally, the patient who would be expected to benefit most from surgery is the young person with progressive enlargement of air-trapping bullae who has minimal or no bronchitis and no clinical or functional evidence of generalized emphysema. Conversely, the least likely candidate for surgery is the older patient in whom the clinical and functional evidence supports a diagnosis of generalized obstructive emphysema with fixation of the chest cage, and in whom the bulla is, in reality, nothing more than a chance roentgenographic finding. Such a patient is managed best by long-term medical therapy. Unfortunately, the bulk of patients do not fall sharply into one group or the other, but present with the variable manifestations previously discussed. In the intermediate group characterized by enlarging bullae, symptomatic bronchitis, and varying degrees of ventilatory and alveolorespiratory insufficiency, it is impossible to generalize on the needs for surgery. Surgery may be advised for all such patients in the hope of correcting the mechanical difficulties due to air-trapping, realizing that the benefits may be very temporary and that generalized emphysema may supervene. It is apparent that some of the difficulties regarding the role of bronchitis can be resolved only with a period of observation. This should include clinical and fluoroscopic observation following adequate treatment of bronchitis and, when possible, simple spirometric studies and a rest and exercise arterial oxygen saturation. In the final analysis, the decision to perform surgery must rest not only upon the results of these observations but also on the understanding of the basic abnormalities of this disease.

Summary

Observations detailed herein suggest that bullous emphysema is an acquired disease due to imperfect communication between bronchioles and alveolar spaces. The relationships between this air-trapping mechanism and symptoms, signs, and functional abnormalities have been described. Because of the individual variations noted, long-term observation has been stressed, which has revealed inconsistency between symptomatology and the extent of bullous emphysema. This has been related to the significant role that bronchitis plays in many of these patients, and a method for appraisal of this factor has been suggested.

Detailed serial pulmonary function studies have revealed that ventilatory insufficiency and hyperventilation are the most consistent findings. A significant, although mild, defect in gas exchange may accompany large air-trapping bullae, but greater abnormalities are undoubtedly due to generalized bronchitis or obstructive emphysema.

Serial observations in some patients suggest that medical therapy designed to control bronchial inflammation may be of definitive value. Equally, it has proved to be of adjunctive value

in surgically treated patients. The decision to perform resectional surgery on a patient with bullous emphysema must be carefully individualized on the basis of the variables described and the theoretic considerations discussed.

Sumario

El Enfisema Vesicular: Estudio a Largo Plazo de la Historia Natural y los Efectos de la Terapéutica

Las observaciones aquí expuestas sugieren que el enfisema vesicular es una enfermedad adquirida debida a imperfecta comunicación entre los bronquíolos y los espacios alveolares. Se describen las relaciones entre este mecanismo para el atrape del aire y los síntomas, signos y anomalías funcionales. Debido a las variaciones individuales que se notaron, se recalca la observación a largo plazo, que reveló incompatibilidad entre la semiología y la magnitud del enfisema vesicular. Esto se correlacionó con el importante papel que desempeña la bronquitis en muchos de estos enfermos, sugiriéndose un método para la justipreciación de este factor.

Estudios pormenorizados en serie de la función pulmonar han revelado que la insuficiencia ventiladora y la hiperventilación son los hallazgos más constantes. Un defecto importante, aunque ligero, en el intercambio de gases puede acompañar a las grandes vesículas atrapadoras de aire, pero las anomalías más grandes se deben sin duda a bronquitis generalizada o enfisema oclusivo.

Las observaciones seriadas en algunos enfermos sugieren que la terapéutica médica encaminada a dominar la inflamación bronquial puede resultar de valor definitivo. Igualmente se ha demostrado que es de valor coadyuvante en los sujetos tratados quirúrgicamente. Hay que individualizar cuidadosamente la decisión en cuanto a la ejecución de la resección quirúrgica en un enfermo de enfisema vesicular, tomando por base las variables descritas y las consideraciones teóricas expuestas.

Resume

Emphysème bulleux: étude à long terme de l'histoire naturelle et des effets de la thérapeutique

Les observations dont les détails sont inclus ici, font penser que l'emphysème bulleux est une maladie acquise, causée par une communication imparfaite des bronchioles et des espaces alvéolaires. Les auteurs décrivent les relations entre ce mécanisme qui retient l'air et les symptômes, les signes et les anomalies fonctionnelles. En raison des variations individuelles relevées, on a mis en oeuvre l'observation à long terme, laquelle a révélé le manque de rapport entre la symptomatologie et l'étendue de l'emphysème bulleux. Ceci a été rapproché du rôle net que la bronchite joue chez beaucoup de malades, et les auteurs ont suggéré une méthode pour évaluer ce facteur.

Des séries d'étude en détail de la fonction pulmonaire ont montré que l'insuffisance ventilatoire et l'hyperventilation sont les données les plus appréciables. Une déficience nette, bien que légère, des échanges gazeux peut accompagner les bulles retenant beaucoup d'air, mais de plus grandes anomalies sont, sans aucun doute, dues à une bronchite généralisée ou à un emphysème obstructif.

Des observations en séries de quelques malades font penser que la thérapeutique médicale prévue pour contrôler l'inflammation bronchique peut avoir une valeur sure. Il a été également prouvé qu'elle avait une valeur d'appoint chez les malades traités chirurgicalement. La décision de pratiquer une résection chirurgicale chez un malade ayant un emphysème bulleux doit être considérée suivant l'individu, avec soin, en se basant sur les variantes décrites, et les considérations théoriques discutées.

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A STUDY OF THE RESPIRATORY EFFECTS OF PREDNISONE IN DIFFUSE AIRWAY OBSTRUCTION[1]

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INTRODUCTION

In severe pulmonary emphysema, treatment with the adrenal corticosteroids or corticotropin is often recommended to relieve some of the airway obstruction (1–4). It is believed that they aid in the relief of bronchospasm, edema, and hyperemia and thereby open the narrow airways that were impeding the flow of air. In addition, steroids are frequently given in the hope of relieving any allergic asthma that might be contributing to the airway obstruction.

The present study was designed to evaluate the effect of prednisone on both the symptoms and pulmonary function tests of patients with pulmonary emphysema. It was thought that by selecting some patients with a considerable "bronchospastic" element it would be possible to find patients who had principally reversible allergic asthma. The typical, brief, periodic asthmatic episode is easily recognized, but chronic status asthmaticus is often difficult to differentiate from pulmonary emphysema as they both manifest diffuse airway obstruction. It was hoped that by studying patients with protracted reversible allergic asthma, it could be determined whether there were any clinical or laboratory findings that would reliably differentiate such patients from those with obstructive emphysema. Bates and associates (5) have reported that the diffusing capacity of the lung is reduced in pulmonary emphysema, in which both tissue destruction and airway obstruction are a factor; but that it is normal in allergic asthma, in which only airway obstruction is present.

"Bronchospasm," as used clinically to denote a diffuse wheezing respiration that changes fairly rapidly in intensity, is frequently a misnomer. The wheezing is just a manifestation of air flowing through narrowed bronchi and bronchioles at a sufficient speed to produce an audible sound. The important factors in its production are rate of air flow and the diameter of the airway. Contraction of the bronchial musculature may or may not be one of the causes of the narrowing of the bronchial tree. Edema, hyperemia, secretions, anatomic distortion, and collapse of air passages by trapping can all result in the narrowing needed to help produce wheezing. As used in this study, the word "bronchospasm" is employed in the clinical sense and is not intended to mean exclusively spasm of the bronchial musculature.

METHODS

The 14 subjects in the study were hospitalized male patients with various degrees of diffuse airway obstruction. They had achieved maximal improvement from the customary therapy with antimicrobial drugs, expectorants, and bronchodilators, and were considered to be in a fairly stable state clinically. All of these patients had dyspnea of many years' duration and 13 had significant wheezing. Many clinicians believed that the basic abnormality in 5 patients (*Chi*, *Dal*, *Sha*, *Gou*, *Zyg*) was allergic asthma. Since the writers were interested in determining the effect of prednisone on "bronchospasm," patients exhibiting this symptom were deliberately selected. Their usual medication was continued unchanged. Only one of the patients had been receiving steroids (*Dal*) prior to the study. He had been on prednisone (10 mg. daily) for many months but, because he still had considerable wheezing and dyspnea and because it was believed clinically that his symptoms were principally due to allergic asthma, the writers wanted to observe the effect of larger doses of prednisone.

The studies were done in the resting state, but fasting was not required. The total lung volume and its subdivisions and the index of pulmonary mixing were determined with the patient reclining, the head of the bed being raised at a 30° angle. The functional residual capacity and index of pulmonary mixing were measured by the seven-minute open-circuit oxygen washout method of Darling, Cournand, and Richards (6). The inspiratory and expiratory flow rates and the maximal breathing capacity were performed in the standing position, using the 13.5-liter Collins respirometer. The maximal midexpiratory flow rate according to the method of Leuallen and Fowler (7), the maximal expiratory flow rate according to the method of Cander and Comroe (8), the inspiratory flow rate, and the one-second portion of the vital

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capacity were determined at a kymograph speed of 32 mm. per second. For the maximal breathing capacity, a kymograph speed of 2.66 mm. per second was used. The gas volumes are expressed at body temperature and pressure saturated with water vapor. In all of the pretreatment studies, the inspiratory and expiratory flow rates and maximal breathing capacity were repeated fifteen minutes following the injection of 0.3 ml. of 1:1,000 solution of epinephrine. Response to epinephrine was not determined following prednisone administration.

The diffusing capacity of the lung for carbon monoxide was determined by the steady state method of Filley and associates (9), using the arterial carbon dioxide tension in the alveolar air equation. The diffusing capacity is given at 0° C., 760 mm. of mercury, dry. The exercise was performed on a stationary bicycle, and it was usually mild because of the poor respiratory reserve of most of the patients. Many patients reached their maximal exercise tolerance. The oxygen consumption during exercise was less than 700 ml. in 8 patients, and only one patient reached 1,000 ml. Oxygen and carbon dioxide content of the blood was determined by the manometric method of Van Slyke and Neill (10); oxygen capacity by the method of Roughton and associates (11). The pH was determined immediately in a closed glass electrode at 37° C. with a Beckman pH meter. The carbon dioxide tension was calculated from the Henderson-Hasselbalch equation.

The symptoms and disability of the patients were estimated on entering the pulmonary function laboratory, using the data sheet from the Veterans Administration Cooperative Study of Pulmonary Emphysema. Prednisone (60 mg. daily in divided doses) was started after the initial tests were completed. The dose was gradually reduced so that by the seventh day the patients were receiving 30 mg. of prednisone daily. At this time, all of the pretreatment tests were repeated except for the residual volume and response to epinephrine.

Observations

Pretreatment Evaluation and Response to Epinephrine

The results of the ventilatory studies are given in table 1 on each patient before and after epinephrine and after one week of prednisone. The resting and exercise arterial blood studies and the diffusing capacity are shown in table 2. Thirteen of the patients had significant wheezing. In 7, the wheeze was almost continuous and, in 6, it was intermittent. If an increase of more than 20 per cent in two or more airflow studies is considered significant, a study of table 1 shows that 7 patients responded to epinephrine although none attained normal values. This 50 per cent incidence of an epinephrine response is probably a falsely high rate since an attempt was being made to find patients who might be in chronic status asthmaticus. All 7 patients increased their maximal breathing capacities, but the other measurements of air-flow rates showed more irregular improvement.

Five of the 7 patients who showed improvement following epinephrine had continuous, and 2 intermittent, wheezes. Five patients were thought clinically to have principally allergic asthma, but only 2 responded to epinephrine. As may be seen from table 1, there is no correlation between the response to epinephrine and the degree of either inspiratory or expiratory airway obstruction. As would be expected, air flow was more compromised on expiration than inspiration. In those who responded to epinephrine, there was in general a greater improvement in expiratory air flow than inspiratory. The amount and character of the wheezing and the response to epinephrine were unrelated to either the ratio of residual volume to total lung capacity or to the index of pulmonary mixing.

The results of the diffusing capacity studies are shown in table 2. The resting diffusing capacity, steady state (D_{co}) is measured to an accuracy of ± 3 ml. per min. per mm. of mercury by the Filley method. Six patients had low resting values between 5.8 and 9.3 ml. per min. per mm. of mercury, while 5 were within the normal range (13 to 22.8). In 3 patients, the diffusing capacity was in the borderline zone. Of the 6 patients with low D_{co}, 2 had responded to epinephrine (*Coo* and *Mur*). Four of the 5 with normal resting D_{co} had responded to epinephrine. Although the diffusing capacity was determined in all patients at rest, one patient (*Mic*) was too dyspneic to attempt exercise studies. Two other patients (*Smi* and *Gou*) were frightened and had considerable difficulty the first time they attempted to exercise on the stationary bicycle. In both cases a leak developed, preventing full collection of the expired air. In fact, one of the patients (*Gou*) had to stop exercising during the expired air and blood collection as he had developed a considerable "bronchospasm," and could barely breathe. After prednisone both of these patients performed their exercise without unusual difficulty. At this time their exercise diffusing capacities were below normal. Whether this improved exercise performance was due to the prednisone or familiarity with the exercise

TABLE 1

VENTILATORY STUDIES BEFORE AND AFTER EPINEPHRINE AND PREDNISONE

Patient	Age	BSA M_2	RV/TLC	Vital Capacity (L)			1 Sec VC (L)			MMF (L/min)			MEF (L/min)			IFR (L/min)			MBC (L/min)		
				C	E	P	C	E	P	C	E	P	C	E	P	C	E	P	C	E	P
Coo	49	1.5	69	1.9	2.5	1.4	0.84	0.85	0.36	16	19	11	24	46	11	137	167	111	20	27	15
Cas	62	2.0	79	1.4	1.2	1.5	0.27	0.22	0.31	11	11	11	11	8	11	141	154	113	22	22	17
Ric	59	1.8	53	4.0	4.0	3.7	1.5	1.0	1.5	51	54	40	102	150	113	169	225	231	54	72	47
Smi	61	2.2	54	2.3	2.5	2.2	0.89	0.81	0.63	24	19	16	46	38	27	118	156	148	40	37	35
Mic	60	1.8	68	1.8	1.6	1.4	0.45	0.45	0.45	16	19	22	22	19	22	89	62	80	20	22	25
Chi	51	2.1	50	3.7	4.0	3.5	2.0	2.4	1.9	64	77	60	224	264	188	298	288	265	65	86	85
Sha	44	1.7	60	2.6	2.6	3.1	1.1	1.1	1.0	43	46	27	70	72	62	145	115	169	45	40	50
Gou	66	1.9	51	2.7	2.8	2.3	1.1	1.1	0.86	29	27	25	67	64	49	206	214	120	42	47	35
Dal	41	1.8	39	3.9	3.2	3.6	2.0	1.4	1.5	51	38	36	186	105	108	353	234	216	97	62	76
Kim	62	2.1	50	2.8	2.8	2.3	1.3	1.3	1.2	32	48	43	96	100	92	170	187	192	54	99	57
Gee	48	1.8	40	3.5	3.6	3.6	2.2	2.2	2.3	97	81	90	199	182	225	332	342	345	99	106	105
Sak	62	1.8	59	2.5	3.5	2.8	0.8	1.3	0.9	22	34	24	44	89	54	150	196	62	35	48	32
Zyg	50	1.6	55	2.9	3.4	2.5	0.94	1.4	0.76	32	51	22	54	105	38	102	185	118	35	69	40
Mur	63	1.6	48	3.0	3.5	2.8	1.6	1.7	1.3	51	54	44	145	174	94	396	383	349	79	101	73

BSA = Body surface area
C = Control period
VC = Vital capacity
P = After prednisone
MBC = Maximal breathing capacity
RV/TLC = Ratio of residual volume to total lung capacity in per cent
MMF = Maximal midexpiratory flow (normal = 270 L/min; SD = 78 (14))
MEF = Maximal expiratory flow (normal = 420 L/min; SD = 143 (14))
IFR = Inspiratory flow (normal = 400 L/min)
E = After epinephrine (determined only in control period)

TABLE 2

STUDIES OF GAS EXCHANGE BEFORE AND AFTER PREDNISONE

Patient	State	D_{co} ml./min./mm. Hg		Oxygen Saturation		P_{CO_2} mm. Hg		Remarks
		Control	Prednisone	Control	Prednisone	Control	Prednisone	
Coo	R	8.8	10.9	94	93	44	47	
	E	13.2	14.9	99	97	53	56	
Cas	R	7.1	8.1	81	87	56	56	
	E	9.6	16.1	79	87	66	64	
Ric	R	20.0	—	96	—	43	—	Refused post-treatment blood studies
	E	22.6	—	100	—	41	—	
Smi	R	7.9	8.5	93	98	47	48	Leak during collection of control—exercise expired air
	E	—	13.8	100	100	57	55	
Mic	R	5.8	6.3	98	97	37	43	Too ill to exercise
	E	—	—	—	—	—	—	
Chi	R	13.0	13.3	100	97	41	40	
	E	24.4	24.2	100	100	48	45	
Sha	R	7.8	11.4	93	93	51	51	
	E	10.8	18.4	95	94	51	60	
Gou	R	11.5	10.8	94	94	46	43	Leak during collection of control—exercise expired air
	E	—	13.2	87	100	58	46	
Dal	R	20.2	15.2	97	99	39	37	
	E	19.5	23.4	100	100	34	39	
Kim	R	16.2	20.3	96	95	42	42	
	E	17.9	19.5	98	99	44	43	
Gee	R	12.4	10.9	97	98	43	43	
	E	14.3	15.3	100	99	29	34	
Sak	R	22.8	24.8	94	93	44	46	
	E	24.7	20.8	93	94	42	45	
Zyg	R	12.0	14.0	93	93	41	40	
	E	19.4	15.3	95	95	48	44	
Mur	R	9.3	9.8	97	97	38	41	
	E	11.5	10.2	98	97	33	42	

D_{co}—diffusing capacity, steady state.
P_{CO_2}—arterial pressure of carbon dioxide.
R—resting.
E—exercise.

procedure it is impossible to state, but one would suspect the latter as there had been no improvement in their low resting values.

Eight of the 13 patients had a definitely diminished D_{co} on exercise (9.6–15.9), and only 2 (*Chi* and *Sak*) reached the low normal range (24.4 and 24.7). Of the 13 patients who performed an exercise D_{co}, only one (*Chi*) showed a significant increase over the resting value (11 ml.). The 3 patients with borderline exercise D_{co} had normal resting values. The 2 patients with normal exercise D_{co} had responded to epinephrine. Patients with normal diffusing capacities at rest or on exercise tended to be among those who responded to epinephrine; however, many patients who responded to epinephrine had low D_{co}. Although in general the lower the maximal breathing capacity the lower the D_{co}, there were many exceptions.

Respiratory Effects of Prednisone

Following a week of prednisone therapy, 8 of the 14 patients noted moderate to marked symptomatic improvement, while 2 patients felt worse. The chief symptomatic response seemed to be a reduction in the distress from wheezing and/or coughing. Many thought their exercise tolerance had increased although their ability to perform the exercise D_{co} on the stationary bicycle left them just as dyspneic as before prednisone therapy (except for *Smi* and *Gou* already referred to). Despite the fact these 8 patients felt moderately to markedly improved, none showed any significant change in the lung volume measurements or in the air-flow rates,

TABLE 3

SYMPTOMATIC RESPONSE TO PREDNISONE VERSUS VENTILATORY RESPONSE TO EPINEPHRINE

	Total	Marked Response to Prednisone	Marked Response to Epinephrine
Symptomatic response to prednisone	8	3	—
Ventilatory response to epinephrine	7	—	2
Response to both	3	1	1

including the maximal breathing capacity. One patient increased his D_{co} while on prednisone therapy (*Sha*). The oxygen saturation increased slightly in 2 patients (*Cas* and *Smi*), both of whom noted symptomatic improvement while receiving prednisone. The carbon dioxide tension was unchanged except in *Gou* whose air flow was so obstructed when the pretreatment exercise blood sample was taken that he was hardly moving any air.

In table 3, the patients who responded symptomatically to prednisone are compared with those who improved after epinephrine. Although 8 patients responded to prednisone and 7 to epinephrine, only 3 responded to both. The same holds true if only the marked response to each is considered, even though the response to the other was only moderate.

Following a week of prednisone therapy, there was a tendency—by no means universal—for the ventilation to increase. The minute ventilation increased in 9 patients and was decreased in 3. The alveolar ventilation increased in 6 and was decreased in 4. One patient (*Ric*) refused post-treatment arterial blood studies. For the entire group of 13 patients, the minute ventilation increased an average of 538 ml. and the alveolar ventilation, 386 ml. Although 7 patients had an increase in their oxygen consumption and 2 had a decrease, the change was even more equivocal: first, because the patients were not studied in a fasting state; and, second, because the change was so small, an average of 13.7 ml.

DISCUSSION

In pulmonary emphysema, as in many other chronic diseases, it is often very difficult to evaluate the effectiveness of any therapeutic measure because of the psychogenic effect of the new procedure itself and the increased attention that the patient frequently receives. In such a situation, patients often state that they feel better, irrespective of the findings on tests that more objectively measure their response. When steroid therapy is used, the evaluation of subjective change is all the more difficult because of the frequent effect of steroids on mood.

In the present study, 8 of 14 patients noted moderate to marked symptomatic improvement after a week of prednisone therapy. This improvement principally consisted of less distress from cough and wheezing. Some seemed to note an increase in their exercise tolerance. When these patients were questioned closely as to the exact amount their wheezing or coughing had diminished, it was difficult to quantitate the change. Those that noted an increased exercise tolerance could do more before having to stop and rest. However, this might not be due to an actual improvement in their clinical state but, instead, might have been a reflection of diminished perception of distress. When the patients repeated their exercise test following prednisone, only 2 (*Smi* and *Gou* as already discussed) actually performed their exercise better than before treatment. That there was no objective evidence of significant improvement in ventilation or gas exchange during prednisone administration was borne out by the failure of any of the ventilatory studies to change and by the fact that only one patient showed improvement in D_{co}, and 2 in oxygen saturation.

It is interesting that there was no correlation between the improvement in air flow following epinephrine and the symptomatic response to prednisone. It might be expected that, if the airway obstruction were due to active inflammation or an antigen–antibody reaction, the relief obtained by epinephrine would be duplicated in the same patients by prednisone. In the present study symptomatic improvement occurred as frequently in those who did not respond to epinephrine as in those who did. This suggests that at the time these patients were studied allergic factors were not contributing to their diffuse airway obstruction and that there was no inflammatory element that was reversible by prednisone. That irreversible tissue damage was present

is suggested by the low diffusing capacities found in these patients, only one (*Chi*) achieving a normal resting value and response to exercise. In this instance, the exercise value is at the lower limits of normal and, perhaps with more strenuous exercise, it might not have been able to increase.

Bates and associates (5) and Williams and Zohman (12) have found that the diffusing capacity is normal in reversible allergic asthma but reduced in pulmonary emphysema with its loss of alveolar and capillary surface area. However, this might not always hold in allergic asthma, as the Filley steady-state D_{so} measures both diffusion across the alveolar-capillary membrane and uneven ventilation-perfusion (9). It was hoped that in the present study this test would differentiate chronic status asthmaticus from pulmonary emphysema. The failure to find any patients with pure reversible chronic status asthmaticus might be a matter of poor criteria for what constitutes asthma as contrasted with pulmonary emphysema (13), or might be due to the fact that the patients were selected for study after achieving maximal clinical improvement. If any of the patients had combined allergic asthma and pulmonary emphysema, probably only the emphysematous element was measured, their asthma having been completely relieved prior to study. Although larger doses and a longer course of prednisone might have been more effective in reversing any allergic element, enough was given to expect considerable demonstrable relief in asthma. It is believed most of the disability in the patients studied was due to anatomic distortion and destruction, the so-called episodes of "bronchospasm" being due to a decrease in the lumen of the airway from air trapping, secretions, and mucosal edema. The bouts of wheezing usually are a reflection of an increase in airway obstruction, but can also occur from a change in the rate of air flow, as in panting respiration during emotional distress.

In this study, prednisone was deliberately given when the patients had reached a stationary clinical state in order that the effect of a single change in treatment could be measured. The effect of steroids during acute exacerbations of the disease was not determined as it is so difficult to evaluate the effect of any one measure when multiple therapeutic modalities are being instituted simultaneously in a situation in which rapid changes can be expected. An additional problem in evaluating the effect of steroids in pulmonary emphysema during acute episodes, especially in severe infections such as pneumonia, is that steroids are believed to help the patient withstand the enormous stress that can be present. Steroids could be life saving in such a situation without directly affecting pulmonary function at all.

The findings in the present study cannot and should not be applied to acute exacerbations of pulmonary emphysema. However, this study does suggest that, once the patient has recovered from an acute episode, continuation of steroid therapy offers little hope of sustaining further real improvement; and long-term steroid therapy is not justified. So often in clinical practice, once steroids are started in an emphysematous patient, they are maintained indefinitely notwithstanding all the dangers of long-term therapy. Although it is possible that the wrong tests were selected to measure any real change in pulmonary dynamics following prednisone, it is more likely that those patients who noted symptomatic improvement had a change only in their threshold of appreciating conscious distress.

Summary

Prednisone was given to 14 patients with chronic pulmonary emphysema who had attained maximal improvement while in the hospital, and a comparison was made between its effect on their symptoms and pulmonary function tests. Although half the patients noted subjective improvement while receiving prednisone, none showed any significant change in pulmonary function tests, including both studies of air flow and gas exchange.

Many patients had considerable "bronchospasm" which was partially relieved by epinephrine. However, it could not be predicted on clinical grounds which patients would respond to a bronchodilator and, furthermore, there was no relationship between epinephrine response and symptomatic improvement during steroid therapy.

The present study was not designed to evaluate the effect of steroids during acute exacerbations of chronic pulmonary emphysema. The failure of prednisone, in fairly high doses, to produce

improvement in any of the objective tests of pulmonary function suggests that long-term steroid therapy is not justified in chronic pulmonary emphysema.

Sumario

Estudio de los Efectos Respiratorios de la Prednisona en la Oclusión Difusa de las Vías Aéreas

Se administró prednisona a 14 enfermos de enfisema pulmonar crónico que habían obtenido en el hospital su mejoría máxima, comparándose el efecto sobre los síntomas y las pruebas de la función pulmonar. Aunque la mitad de los enfermos notó mejoría subjetiva mientras recibía prednisona, ninguno reveló mayor alteración en las pruebas de la función pulmonar, comprendiendo éstas la corriente de aire y el intercambio de gases.

Muchos enfermos tenían considerable "broncospasmo," que aliviaba en particular la epinefrina. Sin embargo, no cabía predecir con razones clínicas qué enfermos responderían a un broncodilatador y, además, no había relación entre la respuesta a la epinefrina y la mejoría sintomática durante la esteroidoterapia.

El estudio actual no se proponía justipreciar los efectos de los esteroides durante las exacerbaciones agudas del enfisema pulmonar crónico. El fracaso de la prednisona, a dosis bastante altas, en producir mejoramiento en alguna de las pruebas objetivas de la función pulmonar sugiere que la esteroidoterapia a largo plazo no está justificada en el enfisema pulmonar crónico.

Resume

Une étude des effets respiratoires de la prednisone dans l'obstruction diffuse des voies respiratoires

De la prednisone fut donnée à 14 malades ayant un emphysème chronique pulmonaire qui atteint une amélioration maxima au cours de l'hospitalisation, et on compara ses effets sur les symptômes aux examens de la fonction pulmonaire. Bien que la moitié des malades nota une amélioration subjective pendant la prise de prednisone, aucun ne montra de changement important des examens de la fonction pulmonaire, y compris des études portant à la fois sur le débit d'air et les échanges gazeux.

De nombreux malades eurent un "bronchospasme" considérable, qui fut levé par de l'épinéphrine. Cependant, on ne put pas prédire d'aprés les bases médicales quels malades répondraient à un bronchodilatateur et, par la suite, il n'y eut pas de corrélation entre la réponse à l'épinéphrine et l'amélioration symptomatique pendant la thérapeutique par les stéroides.

L'étude présente ne fut pas conçue pour évaluer les effets des stéroides pendant les bouffées aigües d'emphysème pulmonaire chronique. Le fait que la prednisone, à des doses passablement élevées, ne réussit pas à améliorer aucun des examens objectifs de la fonction pulmonaire fait penser que cette thérapeutique à long terme par les stéroides n'est pas justifiée dans l'emphysème pulmonaire chronique.

Acknowledgment

The writers are indebted to Mr. Pasquale Cifarelli and Mr. Nicholas Gatto for their technical assistance during this study.

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EFFECT OF QUARTZ POWDER ON TUBERCLE BACILLI AND PHAGOCYTES[1]

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INTRODUCTION

Tuberculosis is believed to be the most common complication of silicosis, and silicotuberculosis is believed to have a poor prognosis. This paper deals with experiments to explain the reason for the rapid multiplication of tubercle bacilli in silicotic tissues.

OBSERVATIONS

Experiment I

Twenty-five mice of *SM* type were chosen for this experiment. One-tenth of a milliliter each of 100 mg. per ml. of saline suspension of quartz powder, bismuth subnitrate, or inulin was injected subcutaneously in the flank. Four hours thereafter, 0.01 mg. of frozen dried BCG (the weight here means that of semi-dried BCG) in 0.1 ml. of saline solution was injected intravenously.

Four mice were killed one day, one week, three, six, and ten weeks, respectively, after the infection. Subcutaneous tissues, when each suspension was injected, were removed and those of one group were put into a mortar to be ground. The resultant paste was suspended in 1 per cent potassium hydroxide solution and cultured on Ogawa[2] glycerol egg medium. Lung tissues of the mice were also cultured by the same method.

BCG contained in 10 mg. of tissue was calculated from the number of colonies grown on the medium, which had been kept at 37.5°C. for four weeks.

As may be seen in table 1, no colony could be cultured from the normal subcutaneous tissue. Ten weeks after the infection, a few colonies of bacilli were cultured for the first time from the region where bismuth subnitrate had been injected. From the site where inulin had been injected, at first only a few colonies appeared on culture; but ten weeks after the infection a relatively large number were cultured. In the case of quartz injection, the number of colonies increased remarkably during the third week, and during the tenth week innumerable colonies appeared.

Relatively many colonies appeared on the cultures from the lungs at both the beginning and the end of the experiment, and a few colonies were visible in the intervening period.

Histologic changes of the subcutaneous lesions produced by quartz dust were studied simultaneously. In the subcutaneous quartz lesion of the mice inoculated with BCG intravenously, a small focus was observed with caseous necrosis surrounded by granulation tissue consisting of mononuclear phagocytes, leukocytes, et cetera. Numerous dust particles, a few leukocytes (figure 1, *A–C*), and a large number of BCG were scattered in the necrotic mass. In the group which was injected with only quartz dust, the central liquefaction necrosis was remarkable and it consisted of quartz dusts, erythrocytes, and a few leukocytes. The necrotic area was sharply demarcated by granulation tissue (figure 2 *A–C*).

Experiment II

Thirty *dd* mice were used in this experiment. One-tenth of a milliliter of a quartz powder suspension containing 50 mg. per ml. was injected into the tail vein of a mouse twice a week for two weeks. Four weeks after the first injection of quartz powder, 0.01 mg. of BCG in 0.1 ml. of 5 per cent glucose solution was injected intravenously.

Each 4 mice were sacrificed one day, and six and twelve weeks, respectively, after the BCG-vaccination. BCG in the spleen, lungs, and liver were cultured on Ogawa's medium with the same method as in *Experiment I*.

As is shown in table 2, many more living BCG were contained in the lungs, spleen, and liver of the mice injected with quartz powder than in those organs of control animals.

Histologic changes of the visceral organs of mice: Lungs. In the mice which received the injections of BCG and quartz dust, there were a small number of epithelioid cell granulomas beneath the

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[2] Composition of Ogawa egg medium:

Basal medium: KH_2PO_4	1.0 gm.
Sodium glutamate	1.0 gm.
Distilled water, in sufficient quantity	100.0 ml.

Two hundred milliliters of whole egg, 6.0 ml. of glycerin, and 6.0 mg. of 2 per cent malachite green are added to 100 ml. of the basal medium. After dispensing into test tubes, the mixture is sterilized once at 90°C. for sixty minutes.

TABLE 1

AVERAGE NUMBER OF BCG COLONIES CULTURED FROM THE SITE WHERE DUSTS HAD BEEN INJECTED

Site of	Slaughter				
	1 Day	1 Week	3 Weeks	6 Weeks	10 Weeks
Inulin injection	6.6	1.4	6.6	3.2	174.2
Quartz injection	13.6	7.2	680.0	42,000.0	168,000.0
Bismuth subnitrate injection	0	0	0	0	1.8
Normal subcutaneous tissue	0	0	0	0	0
Lungs	163.0	9.8	2.4	7.6	81.2

visceral pleura (figure 3). No granuloma was observed in the mice which received the injection of either quartz or BCG alone (figures 4, 5).

Liver: In the mice which received the injections of BCG and quartz dust, granulomas consisting of epithelioid cells were observed in every part of the lobule, in which central hyalinization and the infiltration of a few neutrophils were seen (figure 6).

The formation of granulomas was likewise observed in the mice which received the injection of quartz dust alone, but the size and number of granulomas were smaller than in the mice which received the injection of BCG and quartz dust (figure 7). No granuloma was found in the "BCG-only" group (figure 8).

Experiment III

In this experiment, the influence of quartz, bismuth subnitrate, kaolin, sericite, or carbon particles upon the intracellular multiplication of BCG was studied. For this purpose a tissue culture method was applied.

Two groups of guinea pigs weighing approximately 450 to 550 gm. were used in this experiment. The one group consisted of 4 normal guinea pigs and the other of 6 vaccinated with BCG. For the vaccinated group, 10 mg. of BCG were injected subcutaneously in the right inguinal region and after six weeks a positive reaction (Römer's) was assured. Fifteen milliliters of glycogen saline solution in a concentration of 0.5 mg. per ml. were injected into the peritoneal cavity of nonvaccinated or vaccinated guinea pigs.

Four days later, suspensions of mononuclear cells were obtained by washing the closed peritoneal cavity of the animal with 20 ml. of Hanks balanced salt solution (1) containing a 1:20,000 dilution of heparin. The suspensions were centrifuged at 1,000 r.p.m. for five minutes and the sediment of cells was washed once more with Hanks solution to remove the heparin.

A cell suspension was made with a nutrient medium containing one or two million cells in one milliliter. The nutrient culture medium used in this experiment consisted of 70 per cent of human pleural effusion from tuberculous or cancerous pleurisy, 10 per cent of autogenous serum of the animal, and 20 per cent of Hanks solution. The pH of the medium was adjusted to 7.4–7.6 with 1.4 per cent $NaHCO_3$ solution.

On the other hand, a BCG suspension was made from a 14-day-old culture containing 10 mg. of bacilli in 1 ml. of 1 per cent sucrose solution. The suspension was diluted one hundred fold with Hanks solution and was centrifuged at 1,500 r.p.m. for ten minutes. One volume of this standardized supernatant of bacilli suspension was added to 9 volumes of the cell suspension. The suspension of quartz particles was made as follows: 1 gm. of the quartzite consisting of 99.3 per cent of SiO_2 and 0.09 per cent of Fe_2O_3 was ground into dust in an agate mortar manually, and was suspended in 20 ml. of Hanks solution. This dust suspension was centrifuged at 750 r.p.m. for two minutes. One volume of this supernatant was added to 99 volumes of a mixture of the cell and bacilli suspension.

The suspension of carbon particles was prepared as follows: A liquid ink was prepared from an ink stick, using Hanks solution and was centrifuged at 750 r.p.m. for two minutes. The transmission of its supernatant against Hanks solution employed as a blank was measured with a Hitachi E60-B-type spectrophotometer at 6,100 Å and adjusted to 10 per cent by adding Hanks solution. One volume of this standardized suspension was added to 9 volumes of the culture medium containing cells and bacilli.

The Carrel-flask method was used in this experiment. Five milliliters of the cellular suspension, added to BCG and quartz or other suspensions described above, were poured into Carrel D-5 flasks containing 4 coverglasses (24 by 6 mm.), respectively.

As a control culture, the same volumes of the culture medium were added to the cellular suspension. Flasks were tightly stoppered and kept at 37°C. for cultivation.

The medium was exchanged by aspiration every two days. On the first, third, fifth, and seventh days after incubation, a coverglass was taken out from each flask and the numbers of intraperitoneal

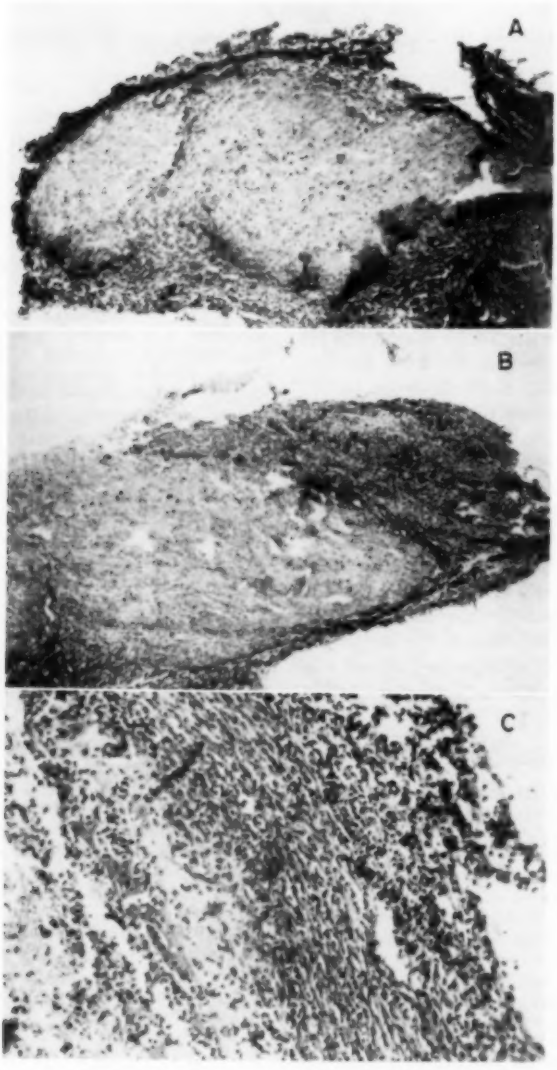

FIG. 1*A–C*. Quartz dust was injected subcutaneously and after four hours BCG was injected intravenously. The mouse was killed six weeks after the injection of quartz dust. Subcutaneous lesion injected with quartz dust. *A*. Caseous mass surrounded by granulation. (× 40) *B*. Same. (× 40) *C*. Higher magnification of the capsular granulation of caseous nodule. (× 100)

mononuclear cells and those of the bacilli in them were counted. Cells were fixed on the coverglass with methyl alcohol for five minutes. Bacilli were stained with Aubert's carbolfuchsin (2) for ten minutes. As discharging fluid, 1 per cent HNO_3 in 70 per cent alcohol was used for about five seconds. Finally, the cells were stained with the usual methylene blue solution and counted microscopically.

Various portions of a coverglass were almost uniform in the distribution of cells. Most of the cells obtained from the intraperitoneal cavity of

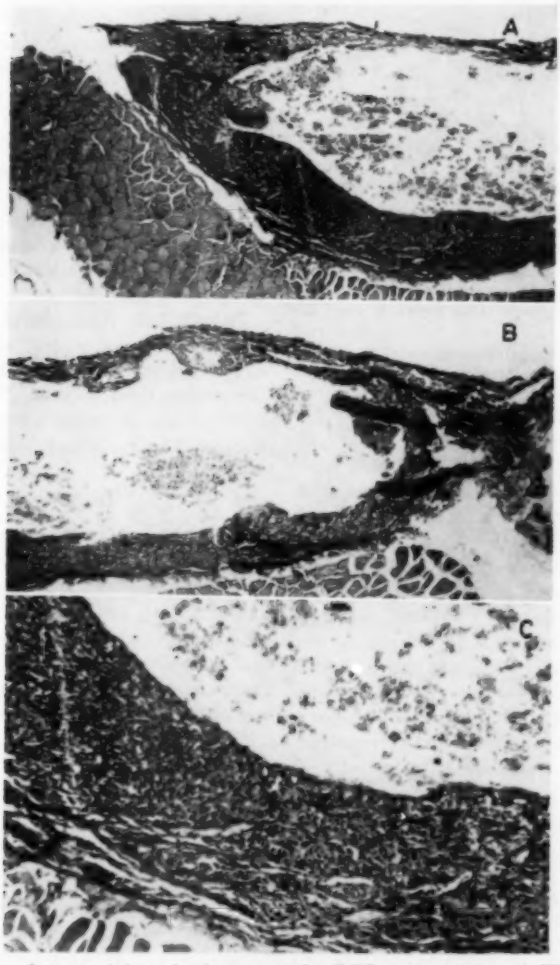

FIG. 2 *A–C*. Quartz dust was injected subcutaneously; BCG was not injected. The mouse was killed six weeks after the dust injection. Subcutaneous quartz lesion. *A*. Sharply demarcated abscess formation. (× 40) *B*. Same (× 40) *C*. Higher magnification of abscess wall. Phagocytic granulation associated with neutrophilic infiltration. (× 100)

nonvaccinated or vaccinated guinea pigs consisted of mononuclear cells. Polymorphonuclear leukocytes and erythrocytes were found in the early stage of the incubation, but they degenerated rapidly and were sometimes phagocytized by mononuclear cells. The measurement of intracellular bacilli was made according to Suter's classification (3, 4). The results obtained from this experiment are presented in table 3, in which it is shown that on the fifth and seventh experimental days more cells with more than 5 bacilli were seen in mononuclear cells with quartz particles than in those with carbon particles or in control cells. Bacilli and dust particles were phagocytized together by mononuclear cells in every case. Cells with quartz particles were round in form, and development of their pseudopods was poor.

In the inner zone of the cytoplasm of the mononuclear cells there were many quartz particles,

TABLE 2

AVERAGE NUMBER OF BCG COLONIES IN 10 MG. OF VARIOUS ORGANS

Organs	Group*	1 Day	6 Weeks	12 Weeks
Spleen	Quartz	316.0	976.0	2,560.0
	Control	151.0	93.8	70.0
Lungs	Quartz	62.7	268.0	2,000.0
	Control	44.3	1.0	0.3
Liver	Quartz	163.0	4,240.0	2,220.0
	Control	178.0	63.8	30.4

* Remarks: (*1*) Quartz group received intravenously 5 mg. of quartz dust twice a week at intervals of three or four days for the first two weeks and was injected intravenously with 0.01 mg. of dried BCG four weeks after the first injection of quartz dust. (*2*) Control group received intravenously 0.01 mg. of the same BCG suspension.

sometimes with BCG organisms. Cord formation or marked multiplication of bacilli was not seen. Degenerative or destructive forms of mononuclear cells phagocytizing quartz were often observed, but in control culture or culture with carbon particles, cells were vivid, and degenerative changes were not found (figures 9–11).

These phenomena were seen not only in normal guinea pigs, but also in those vaccinated with BCG. With respect to the number of phagocytized bacilli, there was no difference between vaccinated and nonvaccinated animals.

Experiment IV

In this experiment influences of dust particles upon mononuclear cells were studied. The test tube method was used. At first, experiments were done with mononuclear cells removed from vaccinated guinea pigs. One milliliter of the cellular suspension, the cellular suspension with quartz or carbon particles, the cellular suspension with BCG, or the cellular suspension with BCG and quartz or carbon particles was put into a test tube. The tubes were stoppered tightly and kept almost horizontal in an incubator. The culture medium was renewed three times a week. The total number of cells was enumerated by Earle's method (5, 6).

The results are summarized in table 4, which shows that the total number of cultured cells in all cases decreased gradually. There is a difference in the decreasing rate of cells between the cellular culture with quartz and that with carbon particles or control, i.e., mononuclear cells with quartz decreased more remarkably than those with carbon particles. BCG did not influence the destruction of mononuclear cells containing quartz or carbon particles, and even in mononuclear cells which did not contain dust particles.

The same experiment was repeated several times, using intraperitoneal mononuclear cells derived from vaccinated or nonvaccinated guinea pigs. Dust particles of carbon, bismuth, kaolin, sericite, or quartz and BCG were added to the mononuclear cells suspension. Cells with quartz, kaolin, or sericite decreased more remarkably than those with bismuth or carbon, as well as the control cells (table 5).

Judging from those results, it seems that dust particles such as quartz, sericite, and kaolin damage host cells remarkably when they are phagocytized by cells. No difference in the survival rate of mononuclear cells can be seen between vaccinated and nonvaccinated animals.

Experiment V

As mentioned in the preceding experiments (*Experiments III* and *IV*), more bacilli are found in mononuclear cells with quartz particles than in control cells, and those cells are easily destroyed when quartz particles are phagocytized by them. But it is not clear whether bacilli multiply in phagocytes with quartz particles or more bacilli are phagocytized by those cells.

To elucidate this question the following experiment was made.

In this experiment, the roller tube method was used. Viable BCG were measured in the following suspensions: cellular suspension with BCG, cellular suspension with BCG and quartz particles, cellular suspension with BCG and carbon particles, culture media with BCG, and suspension of killed cells with BCG. One milliliter of each suspension was put into a test tube in the roller drum, which was rotated at 15 revolutions per hour (r.p.h.) and incubated at 37°C. The culture medium was not renewed in this experiment, but four days later 1 ml. of the new medium was added. Living BCG contained in the cultures were determined by colony numbers on Ogawa solid medium. The culture of BCG was performed on the first and seventh days.

The results presented in tables 6, 7, and 8 show that the multiplication of BCG did not occur in seven days' incubation, but that BCG decreased slightly in all cases. In the experiments listed in tables 6 and 8, all suspensions contained 5.5×10^7 of BCG in 1 ml. on the first day and 4.0 to 2.8×10^7 on the seventh day. In the experiment in table 7, the suspensions contained 3.0×10^7

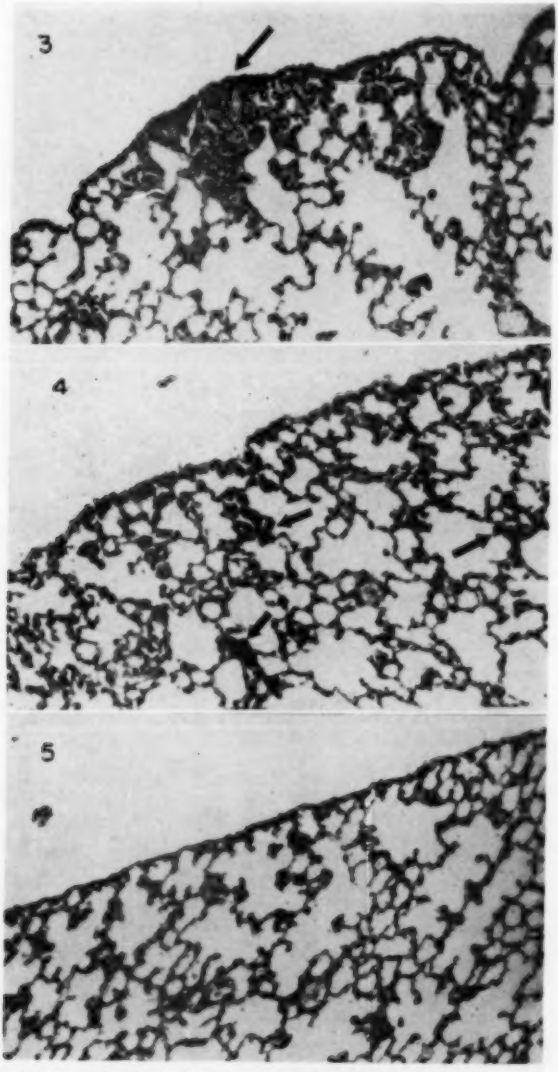

FIG. 3. The lung in the "quartz and BCG" group, killed twelve weeks after intravenous injection of BCG. Arrow indicates a subpleural epithelioid cell granuloma. (× 100)

FIG. 4. The lung in the "quartz only" group, killed twelve weeks after intravenous injection of quartz dust. Arrow indicates irregular thickening of alveolar walls. (× 100)

FIG. 5. The lung in the "BCG only" group, killed twelve weeks after intravenous injection of BCG. No obvious tuberculous changes. (× 100)

on the first day and 7.0 to 17 × 10^6 of BCG on the seventh day. The decreasing rate of bacilli in all cases was almost similar. No multiplication of BCG was observed in this *in vitro* experiment, and actual growth of BCG in the mononuclear cells with the quartz particles does not seem probable.

DISCUSSION

It is believed that silicotic patients are especially susceptible to tuberculous disease and that

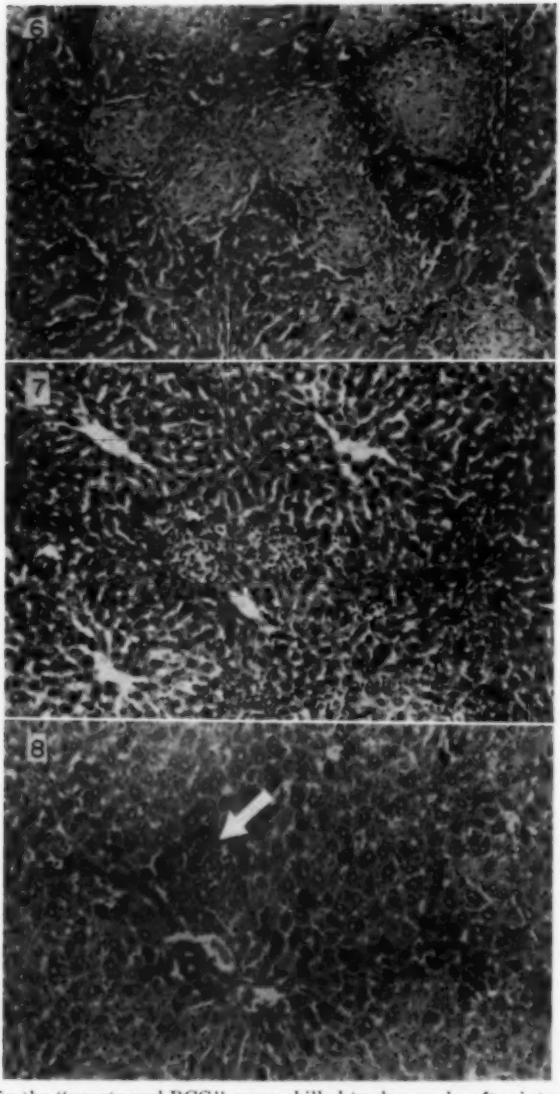

FIG. 6. The liver in the "quartz and BCG" group, killed twelve weeks after intravenous injection of BCG. Proliferation of characteristic granulomas. (× 100)

FIG. 7. The liver in the "quartz only" group, killed twelve weeks after intravenous injection of quartz dust. The granulomatous foci are fewer and smaller than in figure 6. (× 100)

FIG. 8. The liver in the "BCG only" group, killed twelve weeks after intravenous injection of BCG. Cloudy swelling of liver cells and accidental finding of an abortive tubercle. Arrow indicates accumulation of neutrophils. (× 100)

most silicotuberculotic patients have progressive disease. It is also reported that progressive tuberculous processes are caused, even by tubercle bacilli of low virulence, in animals which were given quartz particles for a long time by the intrabronchial route (7–13).

Kettle (14, 15) injected various kinds of dust into mice subcutaneously, and one to three days

TABLE 3

INTRACELLULAR MULTIPLICATION OF BCG CULTURED WITH QUARTZ OR CARBON PARTICLES IN TISSUE CULTURE

Type of Mononuclear Cell	BCG and Kinds of Dust Added in Cultivation	Per Cent of Phagocytizing Mononuclear Cell	Days after Incubation	Per Cent of Cells According to the Number of Bacilli Contained in Them			
				1–2 (Bacilli per Cell)	3–5 (Bacilli per Cell)	6–10 (Bacilli per Cell)	Over 10 (Bacilli per Cell)
Normal*	BCG alone	5	1	88	10	2	0
			3	80	19	1	0
			5	66	29	5	0
			7	58	36	6	0
Immune†	BCG alone	7	1	81	16	4	0
			3	85	12	3	0
			5	83	14	3	0
			7	83	14	3	0
Normal	BCG and carbon‡	6	1	82	15	3	0
			3	81	19	0	0
			5	77	21	2	0
			7	64	32	4	0
Immune	BCG and carbon	8	1	85	14	1	0
			3	84	14	2	0
			5	84	15	1	0
			7	84	15	1	0
Normal	BCG and quartz§	6	1	81	14	4	1
			3	74	22	3	1
			5	53	36	11	0
			7	39	36	14	11
Immune	BCG and quartz	8	1	82	16	2	0
			3	75	19	5	1
			5	49	25	19	21
			7	32	36	21	11

* Normal here means mononuclear cells obtained from nonvaccinated guinea pigs.

† Mononuclear cell donors were vaccinated with 10 mg. of BCG six or more weeks previously.

‡ Carbon particles' suspension was made from liquid ink. The transmission of its supernatant was measured and adjusted to 10 per cent by adding Hanks solution with spectrophotometer.

§ One gm. of quartz particle was suspended in 20 ml. of Hanks solution. This supernatant after centrifugation (at 750 r.p.m. for two minutes) was added to a mixture of cell and bacilli suspension by 1 to 99 in volume.

afterward abundant tubercle bacilli were injected intravenously. He stained many bacilli in the region where crystalline silica was injected. The same experiment was made by the present writers when mice were infected with BCG, growth of which was proved not only by staining but also by a culture method. It was also observed that extensive growth of BCG occurred in the subcutaneous tissue where quartz or sericite powder was injected, but not in the region of bismuth or carbon particles (16).

In case of intravenous injections of BCG and dust, a multiplication of bacilli could be found in the liver, lungs, and spleen when the dust was quartz powder.

It is quite natural that the question would arise whether silica has some growth-promoting effect upon tubercle bacilli. Several experiments were made by the writers, culturing tubercle bacilli on Ogawa medium and in body fluids with quartz dust. But no remarkable growth-promoting effect could be seen. It seems likely that the cause of the phenomenon should be sought in the tissues themselves. Another factor in the activity of phagocytes should be sought.

In the *in vitro* experiments, i.e., tissue culture

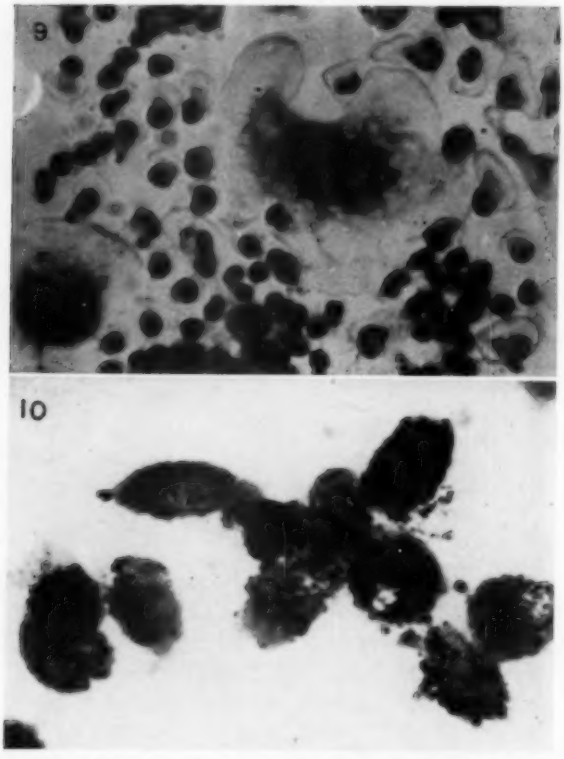

FIG. 9. A 7-day-old intraperitoneal mononuclear cell culture. Polynuclear giant cells are seen in the central and left portions. (× 200)

FIG. 10. A 7-day-old mononuclear cell culture with carbon particles and BCG added. (× 800)

studies, the influences of quartz upon intraperitoneal mononuclear cells of guinea pigs and intracellular multiplication of tubercle bacilli have been studied. It was discovered (Experiment III) at first that intraperitoneal mononuclear cells which have quartz particles in them contain more tubercle bacilli than cells in control experiments; extracellular bacilli were seldom found; and fewer mononuclear cells were seen in BCG-quartz-cell suspension than in BCG-cell suspension. As shown in table 3, mononuclear cells from vaccinated animals phagocytize about the same number of BCG as those from nonvaccinated animals. Concerning the phagocytizing activity, there was no difference between the two groups. But from this experiment it is not possible to know exactly whether multiplication of BCG takes place in mononuclear cells containing quartz particles in cell bodies, or only whether more bacilli are phagocytized by them. Another experiment (*Experiment IV*) shows that quartz, kaolin, or sericite particles damage mononuclear cells when the former are phagocytized by the latter. Furthermore, it may be seen from the last experiment (*Experiment V*) that BCG do not multiply more remarkably in quartz-cell culture or in carbon-cell culture than in control culture.

How can the phenomenon be explained that more bacilli are found in intraperitoneal phagocytes with quartz particles at the end of the *in vitro* experiment, although at its beginning about the same number of bacilli were seen in the cells with quartz particles as in normal cells? The phagocytes containing quartz particles are so easily damaged that, when they also contain bacilli, the latter may go out from the broken cells to be taken in by other cells; consequently cells with quartz particles contain more bacilli than normal cells.

The decrease of the total population of phago-

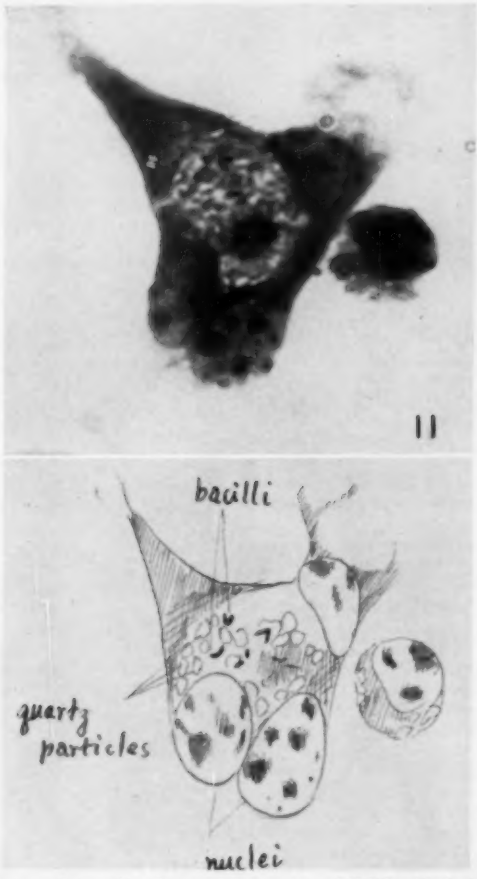

FIG. 11. A 7-day-old mononuclear cell culture with quartz and BCG added. A polynuclear giant cell, phagocytizing many quartz particles and a few bacilli in its cytoplasm are seen. (× 800)

TABLE 4

EFFECT OF VARIOUS DUSTS WITH/OR WITHOUT *BCG* ON SURVIVAL OF MONONUCLEAR CELLS IN VITRO

Type of Mononuclear Cell	BCG and Kinds of Dust Added in Cultivation	Per Cent Survival of Mononuclear Cells (Days after Incubation)			
		1	2	5	7
Immune*	None	100	102	78	68
Immune	BCG alone	100	101	76	65
Immune	Carbon and BCG†	100	112	73	59
Immune	Carbon alone	100	108	69	63
Immune	Quartz and BCG‡	100	80	53	31
Immune	Quartz alone	100	79	32	27

* Mononuclear cell donors were vaccinated with 10 mg. of BCG six or more weeks previously.

† Carbon particles' suspension was made from liquid ink. The transmission of its supernatant was measured and adjusted to 10 per cent by adding Hanks solution with spectrophotometer.

‡ One gm. of quartz particle was suspended in 20 ml. of Hanks solution. This supernatant after centrifugation (at 750 r.p.m. for two minutes) was added to a mixture of cell and bacilli suspension by 1 to 99 in volume.

cytes shown by the addition of quartz particles strongly suggests that the multiplication of BCG in silicotic locus of guinea pigs would be due to a decreased acquired resistance and a high susceptibility of local tissue caused by destruction of mononuclear phagocytes. It may be also assumed that this breakdown of phagocytes can be one factor in the poor prognosis of silicotuberculotic patients.

TABLE 5

EFFECT OF VARIOUS DUSTS AND BCG ON SURVIVAL OF MONONUCLEAR CELLS IN VITRO

Type of Mononuclear Cell	BCG and Kinds of Dust Added in Cultivation	Per Cent Survival of Mononuclear Cells* (Days after Incubation)			
		1	3	5	7
Normal†	None	100	103	73	60
Immune‡	None	100	102	78	68
Normal	BCG alone	100	72	61	59
Immune	BCG alone	100	101	76	65
Normal	BCG and carbon§	100	70	77	64
Immune	BCG and carbon§	100	112	73	59
Normal	BCG and bismuth‖	100	71	72	66
Immune	BCG and bismuth‖	100	61	57	57
Normal	BCG and kaolin‖	100	49	44	30
Immune	BCG and kaolin‖	100	51	23	26
Normal	BCG and sericite‖	100	34	39	26
Immune	BCG and sericite‖	100	47	27	15
Normal	BCG and quartz‖	100	60	31	26
Immune	BCG and quartz‖	100	80	53	31

* Total cell number was counted at each interval by enumeration of cell nuclei. The values indicated survival of mononuclear cells at each time of observation to the total number at one day after incubation.

† Normal means here mononuclear cells obtained from nonvaccinated guinea pig.

‡ Mononuclear cell donors were vaccinated with 10 mg. of BCG six or more weeks previously.

§ Carbon particles' suspension was made from liquid ink. The transmission of its supernatant was measured and adjusted to 10 per cent by adding Hanks solution with spectrophotometer.

‖ One gm. of each dust particle was suspended in 20 ml. of Hanks solution. This supernatant after centrifugation (at 750 r.p.m. for two minutes) was added to a mixture of cell and bacilli suspension by 1 to 99 in volume.

TABLE 6

NUMBERS OF LIVING BCG IN CULTURE MEDIUM WITH LIVING OR KILLED CELLS

Culture	1 Day	7 Days
	ml.	*ml.*
BCG with living cells	5.2×10^7	3.4×10^7
BCG with killed cells		2.4×10^7
BCG with only culture medium		4.0×10^7

TABLE 7

NUMBERS OF LIVING BCG IN NONVACCINATED MONONUCLEAR CELL CULTURE WITH CARBON OR QUARTZ PARTICLES

Culture	1 Day	7 Days
	ml.	*ml.*
Control culture	3.0×10^7	0.7×10^7
Culture with carbon		1.7×10^7
Culture with quartz		0.7×10^7

Control means here the cellular suspension with BCG.

TABLE 8

NUMBERS OF LIVING BCG IN VACCINATED MONONUCLEAR CELL CULTURE WITH CARBON OR QUARTZ PARTICLES

Culture	1 Day	7 Days
	ml.	*ml.*
Control culture	5.5×10^7	2.8×10^7
Culture with carbon		3.7×10^7
Culture with quartz		3.2×10^7

Control means here the cellular suspension with BCG.

SUMMARY

It was observed in mice that quartz particles injected subcutaneously stimulated the growth locally of BCG which had been subsequently inoculated intravenously. However, the multiplication of BCG was hardly observed in the site where nonsilicious particles such as bismuth subnitrate were injected.

The intravenous administration of quartz particles has been shown to increase the susceptibility of mice to BCG when infected by the intravenous route.

In experiments *in vitro*, no multiplication of BCG was observed in the mononuclear phagocytes ingesting dust particles, whereas silicious particles, such as quartz, sericite, or kaolin, destroyed mononuclear phagocytes remarkably.

The results obtained from the present experiments suggest that the heavy destruction of mononuclear phagocytes may be one of the causative factors which enhance extensive multiplication of tubercle bacilli in silicotic loci or produce progressive tuberculosis in silicotuberculotic patients.

SUMARIO

Efectos del Polvo de Cuarzo sobre los Bacilos Tuberculosos y los Fagocitos

Se observó en las regiones subcutáneas de los ratones que las partículas de cuarzo inyectadas subcutáneamente excitaban la proliferación de los BCG que fueron inoculados después endovenosamente. Sin embargo, apenas se observaba multi-

plicación de los BCG en el sitio en que se inyectaban partículas no silíceas, tales como las de bismuto y subnitrato.

La administración intravenosa de partículas de cuarzo aumentó, según se demostró, la susceptibilidad de los ratones al BCG cuando se les infectaba por vía intravenosa.

En los experimentos *in vivo*, no se observó multiplicación del BCG en los fagocitos mononucleares que ingerían partículas de polvo, en tanto que las partículas silíceas, tales como las de cuarzo, sericita o caolín, destruían en forma notable dichos fagocitos.

Los resultados obtenidos en los experimentos actuales sugieren que la intensa destrucción de los fagocitos mononucleares puede ser uno de los factores causantes que acrecientan la vívida multiplicación de los bacilos tuberculosos en los lugares silicóticos o producir tuberculosis evolutiva en los sujetos silicotuberculosos.

Resume

Effets de la poudre de quartz sur les bacilles tuberculeux et les phagocytes

On a observé que, dans les régions sous-cutanées de souris, des particules de quartz, injectées par voie sous-cutanée, stimulaient le développement du BCG qui fut inoculé par la suite par voie intraveineuse. Cependant, la multiplication du BCG fut observée avec difficulté à l'endroit où on injecta des particules n'étant pas à base de silice, telles que du bismuth et du sous-nitrate.

On a montré que l'administration intraveineuse de particules de quartz augmente la sensibilité des souris vis à vis du BCG quand l'infection a lieu par voie intra-veineuse.

Dans des expériences *in vitro*, aucune multiplication de BCG ne fut observée dans les phagocytes mononucléaires ingérant les particules de poussières, alors que les particules de silice, telles que du quartz, de la séricite, ou du kaolin, détruisirent les phagocytes mononucléaires d'une façon remarquable.

Les résultats obtenus dans les expériences actuelles suggèrent que la destruction massive des phagocytes mononucléaires peut être un des facteurs causant l'accroissement de la multiplication vivace des bacilles tuberculeux dans les endroits ayant de la silice, ou causant la production d'une tuberculose progressive chez les malades porteurs d'une silico-tuberculose.

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GENERAL PATHOLOGY OF HUMAN AND CANINE HISTOPLASMOSIS[1, 2]

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INTRODUCTION

The experience of the last fifteen years with histoplasmosis in man and in animals (especially dogs) has resulted in a coherent picture of the pathogenesis of the disease. The causative organism, *Histoplasma capsulatum*, exists in the soil, and its inhalation initiates the infection. A small area of pneumonia develops; in this focus, central caseation occurs regularly. The regional lymph nodes become similarly involved and, with the pulmonary focus, form the primary complex. In man, early hematogenous spread is common, especially to the spleen. Healing of the caseated primary complex and the hematogenous foci by encapsulation and calcification is the rule. In a small number of cases, bronchogenic, lymphogenic, and hematogenic dissemination may occur, resulting in progressive or even fatal acute or chronic disease.

Baum and Schwarz (1) have given a comprehensive diagrammatic representation of the pathogenic relationships between the various types of histoplasmosis in human beings. The epidemic type of the disease did not fit well into the diagram. It was set apart as the possible result of multiple simultaneous "primary" foci following overwhelming exposure. Rubin and associates (2) also described it as the consequence of the increased severity of exposure.

Baum and Schwarz (1) have drawn attention to patients who are "immigrants" to the endemic area. This is an anamnestic detail of importance because the shorter the time of residence in the endemic area, the lesser the probable age of primary infection. It is likely that the age of the patient at the time of primary infection is of considerable importance to the subsequent course of the infection.

In the endemic area, up to 80 per cent of the population becomes infected before the age of eighteen, according to skin tests. Disseminated histoplasmosis is more common at both extremes of life (3), and cavitary histoplasmosis is often a disease of older people, possibly the result of late hematogenous or bronchogenic endogenous reinfection, or the result of exogenous reinfection at a time when the resistance resulting from childhood infection has waned.

The problem of reinfection in tuberculosis has given rise to much controversy. For Terplan (4), the incidental anatomic findings in patients who have not died from tuberculosis have constituted important material for pathogenetic studies on this point. In histoplasmosis, the anatomic residuals of the infection can be identified histologically more easily by the presence of organisms than in tuberculosis (5).

The pathogenesis of spontaneous canine histoplasmosis (6) is similar to that in man. Because of the short duration of puppyhood, however, more "adult infection" is to be expected and the digging and sniffing of dogs makes them prone to more severe exposure. Roentgenographically discrete nodular pulmonary lesions are common in canine histoplasmosis (7) similar to "epidemic" human cases.

This paper deals with the incidentally found histoplasmic lesions in man and dog, with attention focused on the epidemic and the endemic (incidental) type and on the childhood and adult type of infection.

A more complete description of the findings in dogs will be given elsewhere (8). Examination of 30 cats gave completely negative results.

MATERIAL AND METHODS

The material came from 55 autopsies performed in the Jewish Hospital in Cincinnati and from 100 dogs. From the start, puppies were discarded and an attempt was made to obtain older country dogs. The autopsies were carried out as soon after death as possible.

The dissection in the human cases was the same as in a former study (5). The lungs were removed with the trachea, bronchi, and broncho-medi-

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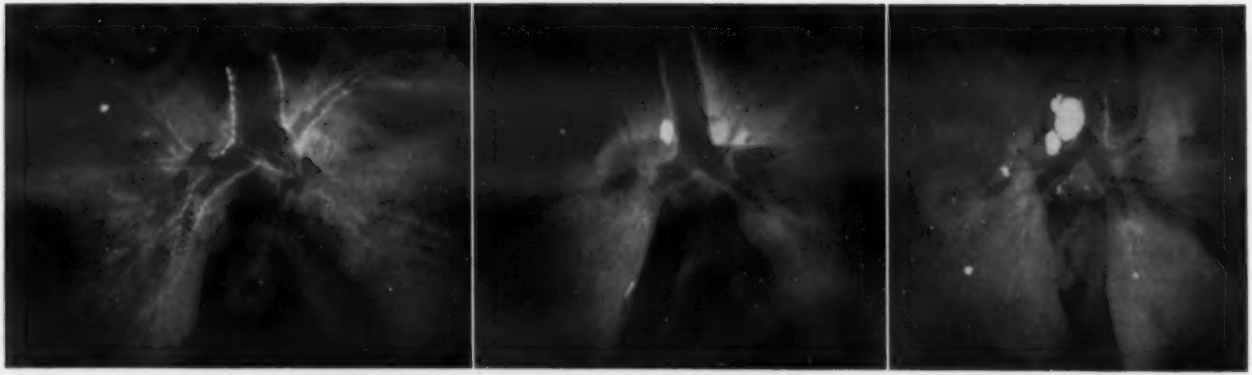

FIG. 1 (Left). D 1008 Dog. Primary focus in lung; no calcification in regional lymph nodes.
FIG. 2 (Center). D 1014 Dog. Classical primary complex with relatively small single pulmonary focus and large calcification in regional lymph nodes.
FIG. 3 (Right). D 1073 Dog. Two heavily calcified primary foci in left lung with a huge calcific deposit in regional lymph nodes. Rather small chalky primary focus in right lung with regional lymph nodes in same state of organization.

astinal lymph nodes attached, and roentgenograms were taken. This facilitated the detection of calcifying lesions, but for noncalcified lesions it was still necessary to rely on careful dissection. The spleens, and in a few cases the livers, were examined roentgenographically. All lesions found were microscopically examined, if necessary, after decalcification. The Grocott and the Gridley stains (9) were used for the demonstration of the organisms, a major improvement over the previous technique (10).

Roentgenograms of the lungs and the spleens of the dogs were obtained, and these organs were examined in the same way as the human organs; in a few instances, the lymph node lesions were cultured.

In the human patients, an attempt was made to obtain data about the duration of their residence in Cincinnati.

Results

Healed primary histoplasmosis in dogs: On roentgenographic examination of 100 cases, one or more calcified foci were found in the lungs of 20 animals; in 11, calcified tracheobronchial lymph nodes were also present. In all dogs, the spleens revealed no abnormalities on morphologic or roentgenographic examination.

The pulmonary foci measured from 1 to 3 mm. in diameter, and most were situated subpleurally. The pleura adjacent to the lesions showed a button-like gray fibrous thickening. The foci had a white, chalky center and a grayish hyaline fibrous capsule that in many cases was broad and conspicuous. Some of the chalky calcified lymph nodes were quite large (figures 1–3). A few foci were caseated and only slightly calcified. In such a case, Histoplasma was cultured from a lymph node.

Organisms morphologically representative of *Histoplasma capsulatum* could be easily demonstrated, often in great numbers, in the decalcified lesions (figure 4).

On both macroscopic and roentgenographic examination, the pulmonary histoplasmic foci were readily distinguishable from the multiple small alveolar osteomata that are so frequently found in the lungs of old dogs and which can be extracted from the tissue easily since they have no capsule.

Slightly calcified histoplasmic foci have to be differentiated from small nodular pneumonias.

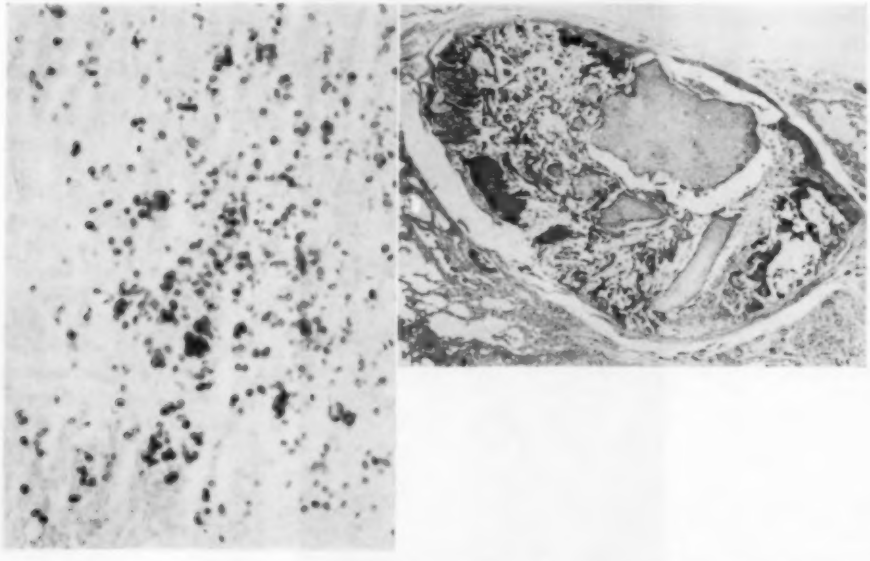

Fig. 4 (Right). D 1014 Same dog as figure 2. Grocott stain: innumerable organisms of uniform size and shape of two to five μ in diameter. *Histoplasma capsulatum*, in primary focus. (800 ×)

Fig. 5 (Left). D 1008 Same dog as figure 1. Primary focus with complete liquefaction necrosis and subsequent calcification. Some calcified particles appear to be floating in the debris where cholesterol clefts are clearly visible. (30 ×)

These pneumonias in some cases were caused by worms; in other cases their nature remained obscure. Some were suspected of being acute pulmonary histoplasmosis, although no organisms could be visualized in sections. In one such case in the present series and in several in a subsequent study, *H. capsulatum* was cultured from the corresponding lymph node.

Histologically, the histoplasmic pulmonary foci were very similar in structure. They consisted of calcified necrotic tissue floating in amorphous chalky material in which many cholesterol clefts could be recognized (figure 5). The lesions had fibrotic capsules containing lymphocytes and mononuclear or epithelioid cells. Often the capsule was hyaline in appearance. If multiple pulmonary foci were present in one dog, they were identical in structure. In one case, a slightly calcified caseous spread was found along bronchi in the vicinity of heavily calcified foci. Organisms were present most abundantly in the calcified necrotic particles. They were absent or scarce in the chalky debris. The general structure of the lymph node calcifications was the same as that of the pulmonary foci.

The number of pulmonary foci in the dogs with or without lymph node involvement is given in table 1. If less than five pulmonary foci were present, the lymph nodes were free of demonstrable lesions in half of the cases. When more than five pulmonary foci were found, in nearly all cases the lymph nodes were extensively involved.

In cases of only one calcified pulmonary focus and similar lesions in the hilar lymph nodes, the nature of the primary complex can readily be recognized. Comparable single pulmonary foci without lymph node involvement may be regarded as the primary foci of an incomplete complex. In cases of more than one pulmonary focus, the principle of the primary complex is sometimes still recognizable. When great numbers of pulmonary foci with involvement of lymph nodes are present, their identical size and structure in the absence of hematogenous dissemination to the spleen or elsewhere indicate that they originated simultaneously as the result of one massive aerogenous infection and, therefore, are multiple primary foci (figures 6, 7). The histoplasmic primary focus in dogs (and in man) is often characterized as an acinous, or at most, a lobular pneumonia with subsequent caseation, calcification, and encapsulation.

TABLE 1

NUMBER OF HEALED PULMONARY HISTOPLASMIC FOCI AND LYMPH NODE INVOLVEMENT IN 20 DOGS

Number of Pulmonary Foci	Lymph Nodes	
	Negative	Positive
1	4	3
2	—	1
3	2	1
4	2	2
6	1	—
7	—	1
10	—	1
More than 10	—	2

Healed or healing human primary histoplasmosis: Roentgenography was used as a quick method to detect pulmonary and splenic calcified foci. All lesions found macroscopically were histologically examined. In a high percentage of the 55 unselected cases, healed or healing primary histoplasmosis was present. The results are summarized in table 2 according to the birthplaces of the patients.

Quantitatively there was no difference between the patients born in the endemic area or outside of it. In both groups the number of positive cases reached the very high figure of 84 to 87 per cent, respectively. Qualitatively, however, there was a big difference. In the patients born in the endemic area, with one exception, only calcified primary complexes were found. Among the 14 positive cases in patients born outside the endemic area, there were 7 with noncalcified or slightly calcified dry caseous lesions which were quite different from the "ordinary" healed primary complexes. In 2 other patients who had lived for six and forty-two years, respectively, in the endemic area, the distal nodes of the tributary chain of lymph nodes of the primary complex were caseated and not yet calcified. These lymph nodes were cultured because they were believed to represent the result of rather recent infection; but no organisms could be isolated. One 60-year-old patient, who was born in Virginia but had been living in Cincinnati for thirty-four years, had four chalky apical foci without lymph node involvement.

On the roentgenogram, usually one large primary focus was present. Twice there were two, once four, and once there were five primary foci. In the vicinity of some primary foci, a number of

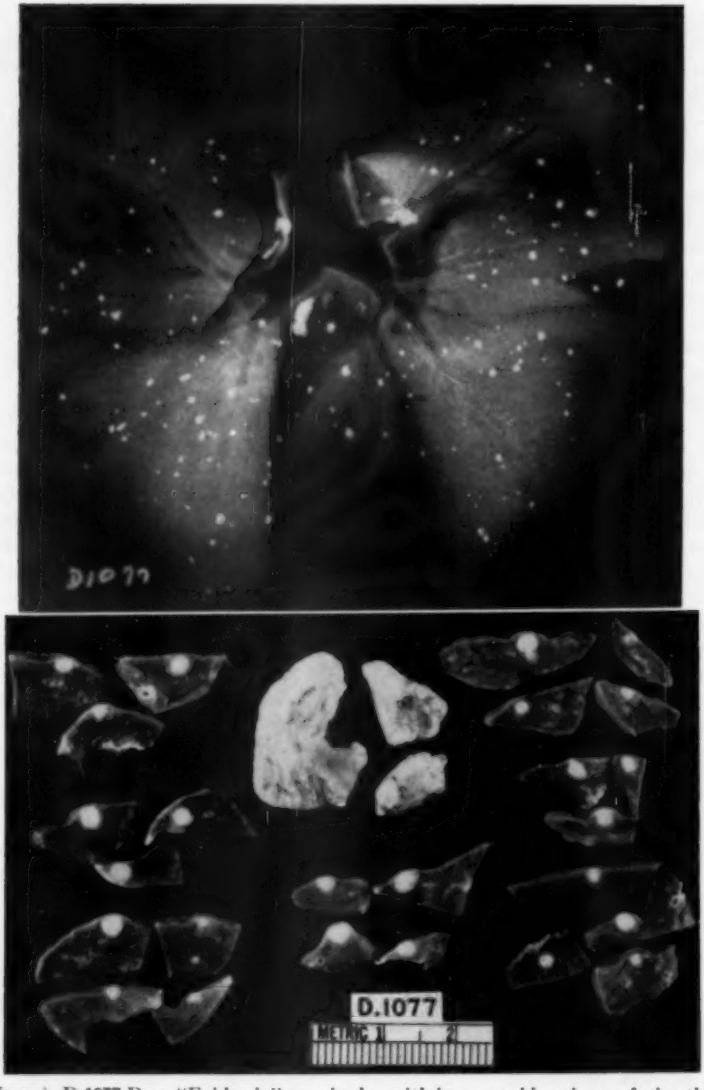

FIG. 6 (Upper). D 1077 Dog. "Epidemic" case in dog with innumerable primary foci rather diffusely scattered through both lung lobes; lymph nodes affected.

FIG. 7. (Lower). D 1077 Same dog as figure 6. Some of the primary foci have beeen removed and sectioned and show subpleural localization, essentially uniform size, and bulging of the pleura in many instances. Calcified lymph nodes.

smaller satellite lesions were present (figure 8). Microscopically, these proved to be minor calcifications in the pleura and interstitial lung tissue, consequences of local lymphogenous dissemination. A few satellite lesions were situated in the pulmonary tissue proper as demonstrated by the elastic skeleton in the calcified material. Most often the primary foci were situated subpleurally. Often the pleura above the primary focus showed pleural thickening identical to that seen in the

TABLE 2

PRIMARY HISTOPLASMOSIS IN 55 CONSECUTIVE AND UNSELECTED AUTOPSIES IN ADULTS

Patient's Birthplace	Histoplasmosis	
	Present	Absent
Ohio	26	2
Kentucky	7	3
Missouri	—	1
Total endemic area	33 (84.6%)	6
Northeastern United States	5	
Southeastern United States	4	1
Illinois	1	
Foreign	4	1
Total nonendemic area	14 (87.5%)	2

dogs (figures 9, 10). Local pleural adhesions were not a feature of healed primary histoplasmosis in either species.

The involvement of the lymph nodes draining the primary focus was very extensive in nearly all cases.

Microscopically, ossification and bone marrow formation were regularly found in the primary foci and in the lymph nodes. In all cases, especially in the pulmonary foci, typical organisms were present somewhere in the calcifications, often in large numbers.

The routine roentgenographic examination of the lungs at necropsy focused attention to a greater extent on the presence of satellite lesions. In some cases, it was difficult to indicate which of the scattered small calcifications was the primary focus proper.

In 7 patients born outside the endemic area, noncalcified or slightly calcified dry caseous lesions were found (table 3, figure 11).

This type of infection probably took place during adult life and is strikingly different from the findings in persons born in the endemic area. In the last case, the patient must have escaped

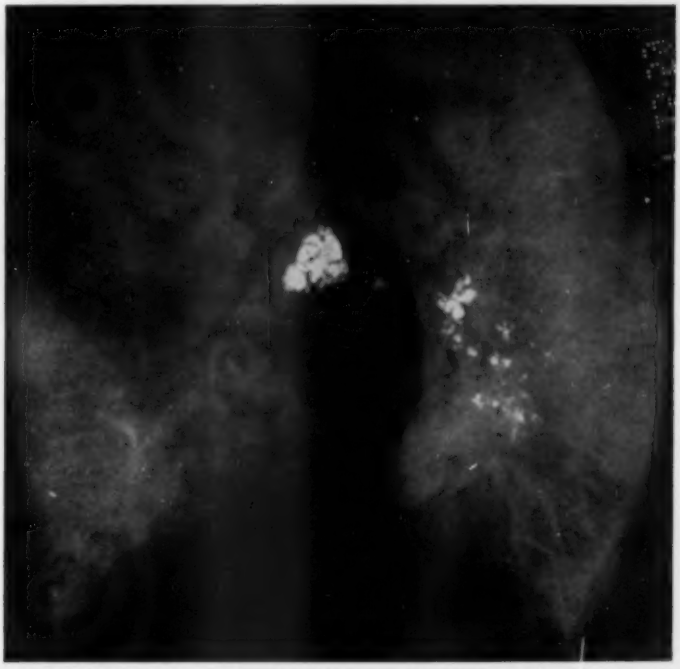

FIG. 8. D 1043 W. F. (13 years) Histoplasmic primary complex. Primary focus in right lower lobe. The focus is surrounded by multiple foci of calcification which are in part in the interstitium of the lung and in part in the pleura. The multiplicity of satellite foci makes it almost impossible to specify which of the foci is the primary lesion. Notice stippling of calcific deposits in regional lymph node.

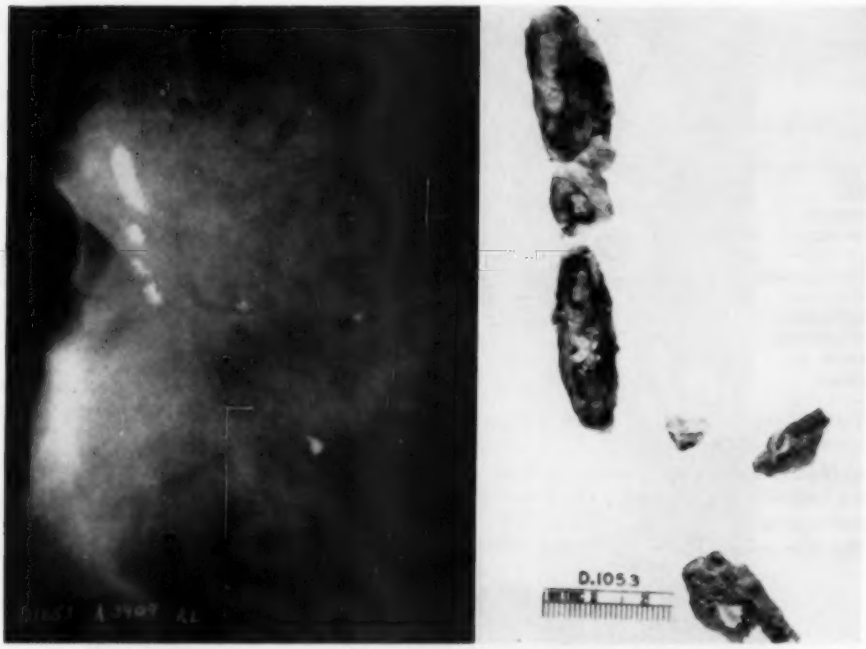

FIG. 9 (Left). D 1053 W. F. (38 years) Histoplasmic primary complex. Right lung with sharply circumscribed calcified primary focus in lower lobe, and chain of affected lymph nodes. The first is in the pleura, the next are in the interlobar space and finally in the hilus.

FIG. 10 (Right). Same case as figure 9. The chain of lymph nodes corresponds exactly to the roentgenogram.

TABLE 3

PRESENCE OF NONCALCIFIED CASEOUS LESIONS IN "IMMIGRANTS" TO THE ENDEMIC AREA OF HISTOPLASMOSIS* WHO DIED OF LESIONS OTHER THAN HISTOPLASMOSIS

Number	Age, Race, Sex, Birthplace	Moved to Endemic Area at Age	Anatomic Findings
1 D 1002	78 WF Germany	48†	D.c.pr.f. RUL + corr. l.n.
2 D 1026	59 WF New York	47	D.c.pr.f. RLL + corr. l.n.
3 D 1062	58 WF New York	46	Slightly calcified D.c.pr.f. RUL + corr. l.n. + 10 active (noncalcified) foci in spleen
4 D 1164	51 WF Massachusetts	31	Slightly calcified D.c.pr.f. LUL + corr. l.n.
5 D 1167	50 NF Alabama	17	D.c.l.n. (no primary focus found)
6 D 1225	67 NF Alabama	25	D.c.pr.f. LUL + corr. l.n.
7 D 1152	62 WM Russia	32	Conglomerate of D.c. small foci RML + corr. l.n.
8 D 1200‡	76 WM Ohio	70	D.c.pr.f. RML + corr. l.n. + caseated foci liver and spleen

D.c.pr.f. = Dry caseous primary focus
corr. l.n. = corresponding lymph node in similar condition
RUL = right upper lobe
RLL = right lower lobe
RML = right middle lobe
* *H. capsulatum* was morphologically demonstrated in all lesions mentioned in the table.
† Worked on chicken farm.
‡ Lived from 1906–1954 in Massachusetts.

infection as a child but not as an old man, when he returned to the endemic area to live on a farm.

Splenic calcifications were found in 28 cases (figure 12). In one patient, the splenic disseminations were not calcified. The 29 cases of splenic dissemination occurred in 43 completely examined positive cases (67 per cent). Of 30 positive cases of patients born in the endemic area, 22 (73 per cent) had "positive" spleens; of 13 positive cases of patients born outside the endemic area, the spleens were positive in 7 (54 per cent). The figures are too small to make the difference statistically significant. Slight and extensive splenic dissemination occurred in both groups.

There seems to be some parallel between the extent of the primary complex in the lungs and

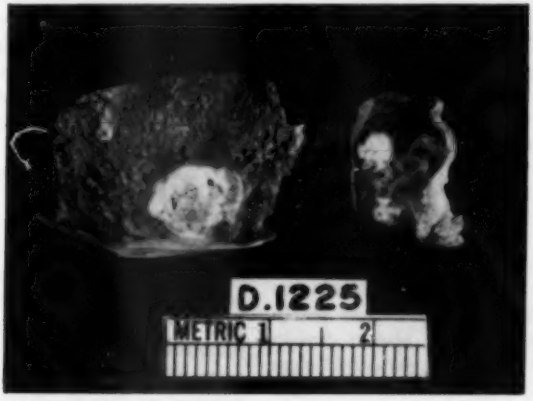

FIG. 11. D 1225 C. M. (67 years) Adult infection type of histoplasmic primary complex. Caseous primary pulmonary focus with caseous lymphadenitis.

FIG. 12. D 1190 W. M. (74 years) Spleen with innumerable calcific foci, some several centimeters in diameter. These are the largest calcifications ever seen by the writers in the spleen.

the extent of the dissemination in the spleen. In a patient with focal bronchiectasis and a histoplasmic broncholith, uncountable splenic calcifications were present. Other massively positive spleens were found in patients with many satellite lesions scattered around the primary focus.

In a few cases, roentgenographic examinations of the liver were made. Only once was a heavy hepatic dissemination observed. Hepatic dissemination in most cases was slight. Lately, in selected cases, roentgenograms of kidneys and adrenals were also obtained, but no abnormalities were found.

Discussion

Canine and human histoplasmosis in many respects resemble each other, with identical pathogenesis and epidemiology. Histoplasmin tests in dogs and lymph node cultures from sacrificed animals have shown how widespread the canine infection in the endemic area can be. In Kansas and Missouri, the histoplasmin test in 102 dogs was positive in 14 per cent. In 22 dogs eight years of age and older, 23 per cent of the cases were positive (11). In Loudoun County (Virginia), 145 of 397 dogs (36 per cent) proved infected by culture of peribronchial lymph nodes (12). The percentage of infected dogs, however, has never been found to be as high as that in some human populations in the endemic area. In these, 80 per cent or more of persons eighteen years and older may react positively to histoplasmin. The shorter life span of the dog is probably responsible for this difference.

The present figures, based on anatomic studies, are in accordance with other epidemiologic data. In the present series of 55 patients, 47 (85 per cent) proved to be infected. In a previous study, 67 per cent were found to be positive (5). The increased prevalence in the present study is attributed to the use of screening by roentgenography and to the Grocott methanamine silver stain. Twenty (20 per cent) of 100 dogs showed healed or healing histoplasmic lesions. In a subsequent study, when cultures were systematically taken, results similar to the ones described by Emmons (12) were obtained.

The mean age of patients born in the endemic area was sixty-three years. The patients who were born outside the endemic area had resided there for periods from six to more than fifty years, with a mean of approximately thirty-five years. In both groups, about 85 per cent of the patients were found to be infected. Apparently, the infection rate during childhood does not differ essentially from that during later adult life. The adult "immigrant" in the long run, like the native child, does not escape infection.

It is impossible to state exactly the age of the dogs in the present study; a mean age of five or six years is a rough estimate. In the human cases, four times as much healed histoplasmosis was found as in the dogs. The mean time of exposure, however, in the humans was some five to ten times that in the dogs and amounted to thirty-five or sixty-three years as against only five or six years in the dogs. This indicates that the infection rate in dogs in Cincinnati is higher than that in man.

The patients in the autopsy cases were mostly city dwellers, presumably with incidental exposure and not the overwhelming epidemic exposure of the "rural chicken house." This resulted in a single or, at most, a few primary foci. In the present 47 infected patients, more than one primary focus was found in only four instances. In a former series with 70 positive cases, the number of multiple primary foci was the same (5). In the dogs, however, multiplicity of primary foci was very frequent; in 13 of the 20 dogs, there was more than one primary focus, and in 5 of them there were more than five.

Infectious dust can carry only a small dose of organisms deep enough into the air passages to initiate a peripheral pulmonary lesion such as the primary focus. More severe exposure will not give larger lesions but rather more numerous lesions (multiple primary foci). Individually, they do not differ from the incidentally acquired single primary focus. Only their multiplicity indicates the severe exposure—proof of the higher concentration of infectious material to which dogs are exposed as compared with the average human being. In 2 dogs, the healed residuals of the "epidemic" type of histoplasmosis with its very numerous primary foci were observed.

In human beings, multiplicity of primary foci can also be used as an indication of massive exposure. The following are a few pertinent observations not included in the unselected consecutive series of cases.

In a 71-year-old patient dying from pancreatic carcinoma, there were some 40 or 50 calcified primary foci, diffusely scattered through both lungs; and in a 48-year-old patient dying from

cavitary histoplasmosis, seven calcified and ossified primary foci were noted. Both patients had been farmers in the endemic area. In a clinical case of a 16-year-old boy with diffuse nodular pulmonary histoplasmosis, a pulmonary biopsy showed multiple primary foci. The onset of the disease occurred two weeks following the cleaning of a chicken house. After one year, the nodular lesions appeared slightly calcified. This is distinctly a case of primary histoplasmosis of the epidemic type.

Rubin and associates (2) classify the epidemic type as a benign form of the disease. Their nine patients with culturally proved diffuse nodular acute pulmonary histoplasmosis all recovered. Three of these were definitely epidemic cases. Among the more than 400 epidemic cases compiled by Lehan and co-workers (13), only five were fatal, and four of these were in young children. Silverman and associates (14) described two of these cases in siblings of two and four years of age living on a farm. There had been intensive exposure in a dirty chicken house. Anatomically, however, there were no indications that massive infection was the cause of the malignant course of the disease. In the 2-year-old girl, two pulmonary primary foci were found; in the 4-year-old girl, there was only one primary focus. The patients died from disseminated histoplasmosis. Younger age groups in general are predisposed to widespread dissemination in histoplasmosis (3). In a girl of seventeen with exfoliative dermatitis, Silverman and associates (14) saw extensive histoplasmic dissemination during treatment with adrenal cortical extract. In the lungs, again only one primary focus was present. In these cases, dissemination apparently had more to do with lack of "natural resistance" than with size of infective dose.

Likewise, in dogs, the epidemic type of the disease as such does not seem to be especially malignant, and multiple primary foci with severe dissemination to the lymph nodes may heal completely. In spite of extensive involvement of the tracheobronchial lymph nodes in dogs, involvement of the spleen has never been found. In sharp contrast with human histoplasmosis, splenic calcifications are not a feature of healed canine histoplasmosis.

Emmons and co-workers (12) cultured Histoplasma from lymph nodes in 30 to 40 per cent of dogs in Loudoun County (Virginia). Robinson and Kolcher (15), on the other hand, in a culture series of 300 dogs in Lexington, Kentucky, did not find the organism in the spleen or bone marrow in a single instance, even if canine histoplasmosis has regularly been observed in Lexington. These negative splenic cultures and the present negative splenic roentgenographic findings indicate that dogs possess some natural resistance against hematogenous dissemination.

In human histoplasmosis, most infected persons experience hematogenous dissemination to the spleen. In more than 60 per cent of positive cases, healed splenic calcifications were found. In the spleen of two healed human "epidemic" cases, there were no calcifications in one and only a few in the other; therefore, the nodular pulmonary lesions represent uncomplicated primary histoplasmosis and, in a patient with unimpaired natural resistance, the infection almost always takes a benign course.

Conceivably, part of the natural resistance in dogs may be ascribed to the fact that the infection generally takes place during adult life. Not only hematogenous dissemination but, in many cases, even lymphogenous spread to the hilar lymph nodes is absent.

In human patients, primary histoplasmic infection occurring during adult life often took a course different from that resulting from childhood infection. In one of the cases, the lymph nodes were uninvolved; in others, the lymph node involvement remained restricted to one node. This is in marked contrast to the childhood type of healed primary histoplasmosis with its extensive lymph node involvement (5).

In the human patients who were infected during adult life, the histoplasmic primary complex was a dry caseous lesion with little or no calcification. The lesions were easily cut with a knife. In dogs, similar lesions were not encountered. The lack of calcification is not due to the early age of the lesions, since they do not show any sign of activity histologically, and a few attempts at culture were unsuccessful. Calcification had been simply sluggish. The same is well known in chronic bilateral fibrocaseous histoplasmosis that accompanies cavitary histoplasmosis. In histoplasmosis, however, this type of caseation may be found already in the primary lesions acquired during adult life.

In some of the cases, the primary pulmonary focus of the adult infection type could well be described as a "coin lesion" or as a histoplasmoma. The histoplasmoma is a distinct clinical

and anatomic entity. Its pathogenesis is still a matter of dispute. Baum and Schwarz (1) put it in a pathogenetic group together with cavitary histoplasmosis. Rubin and associates (2), analyzing 123 proved human clinical cases of histoplasmosis (all but two patients living in the endemic area) do not even mention the histoplasmoma, probably because most of their cases came from a tuberculosis sanatorium and consisted of cavitary histoplasmosis. In another publication from the same region (16), two typical cases of histoplasmoma are described, and Sweaney (17) mentions two more—one, however, without organisms. Considering the number of cases reviewed, this represents a meager harvest. This is the more remarkable because outside the endemic area the histoplasmoma most dramatically has drawn attention to the disease (3, 18, 19).

With the present observations about the caseous adult infection type of primary histoplasmosis in mind, some of the Cincinnati cases of histoplasmoma and cavitary histoplasmosis were studied with respect to birthplace and age. It was found that many patients with histoplasmoma were born outside the endemic area and most patients with cavitary histoplasmosis had been born within the endemic area.

In those cases in which the patient was born outside of the endemic area, it is reasonable to assume that the histoplasmoma was the result of primary infection during adult life and not a "late bronchogenic" dissemination, as suggested by Baum and Schwarz (1). The same can be concluded from other studies (3, 18). Puckett's (3) adult patients had been in the endemic area for one to twenty years; Greendyke's (18) patients were not from the endemic area proper but from its "outskirts."

The difference in the mean age of patients with a histoplasmoma and of patients with cavitary histoplasmosis is another reason to distinguish between the two. Histoplasmoma is a disease mainly of adults less than fifty years of age (3, 18, 19). The five patients of Baum and Schwarz (1) were thirty-seven, forty-one, forty-nine, fifty-nine, and sixty-four years old. In contradistinction, cavitary histoplasmosis is mainly a disease of people from fifty to sixty (20). The patients of Baum and Schwarz (1) were forty, forty-one, sixty-one, sixty-two, sixty-five, seventy, and seventy-six years of age. Seventy per cent of the 90 patients of Rubin (2) were more than fifty years old. Therefore, cavitary histoplasmosis is a late manifestation of the disease while histoplasmoma is not. Neither is the histoplasmoma a precursor of cavitary histoplasmosis. In many cases, histoplasmoma has to be regarded as a clinical variety of the adult type of infection with *Histoplasma capsulatum*. Cavitary histoplasmosis, being often a late manifestation of the disease after childhood infection, may be the result of exogenous reinfection.

The advanced mean age of the patients with cavitary histoplasmosis suggests reinfection as its cause. Endogenous reinfection with organisms having remained dormant in the primary complex for half a lifetime is a possibility. The organisms in the lesions remain histologically recognizable virtually indefinitely. However, from surgical excision of solitary foci (3) and in autopsy material, the fungi could not be cultured (5) and, therefore, were considered dead and petrified.

Exogenous reinfection is a second possibility. In an individual case it will often be impossible to decide between the two possibilities. The following case reports represent reinfection in histoplasmosis.

Case 9 (D 1000). The patient was a white, 78-year-old male, who was born in Cincinnati and died from intestinal infarction. A calcified primary focus with ossification, bone marrow, and many typical organisms was found subpleurally low in the lower lobe of the left lung, with a corresponding lower tracheobronchial lymph node. In the apex of the lower lobe of the right lung, a fibro-anthracotic-caseous lesion of about 0.5 cm. in diameter was found.

This life-long resident of the endemic area had a typical histoplasmic primary complex of the childhood infection type in one lung and, in the other lung, a histoplasmic lesion of the adult infection type without lymph node involvement.

Case 10 (D 1228). A 79-year-old man, a long-time resident of the endemic area, had an old calcified histoplasmic primary complex with multiple calcified splenic disseminations. In the vicinity, but nevertheless separated from the primary complex, a dry caseous practically non-calcified complex of the adult infection type was found.

Each of these two patients showed two histologically proved histoplasmic processes of distinctly different type and age.

It cannot always be decided whether additional caseous pulmonary foci such as were found here represent endogenous or exogenous reinfection. The older calcified lesions were the result of child-

hood infection. In the endemic area, the primary complex nearly always is acquired before the age of eighteen, but exposure is a constant danger in the endemic area. There are many arguments for exogenous reinfection in the two cases mentioned, such as the fact that one of the patients kept chickens during the last years of life, an environment often associated with histoplasmic infection.

The watertower epidemic in Eden Park in Cincinnati can be used as epidemiologic proof that exogenous reinfection in the endemic area is possible (21, 22). Here a group of adults, at least in part born in the endemic area, were severely exposed to spore-containing dust and showed diffuse nodular pulmonary disease shortly after exposure. There is anatomic (unpublished) evidence that the disease indeed was acute pulmonary histoplasmosis of the epidemic type. The puzzling fact that the pulmonary lesions did not calcify in the course of the years is in accordance with histoplasmic infection during adult life. Older pulmonary calcifications were found at autopsy in one of the group fourteen years after the "epidemic" occurred. In the mountain home (Arkansas) epidemic, in some cases exogenous reinfection has also been very likely, though not proved (23). In the future, more specific information will be necessary.

For the clarification of the etiology of cavitary histoplasmosis, an evaluation of the role of exogenous reinfection may be of practical importance.

Summary

In 55 consecutive autopsies performed on adult patients in Cincinnati, Ohio, who had had diseases other than active histoplasmosis, healed primary histoplasmosis was found in 47 (85 per cent). Healed or healing lesions of primary histoplasmosis were found in 20 (20 per cent) of 100 dogs from the Cincinnati area.

Roentgenograms of the lungs and spleens proved helpful in demonstrating the lesions. The histoplasmic nature of the lesions in all cases was diagnosed microscopically on the basis of the presence of organisms of the size, shape, and staining qualities of *Histoplasma capsulatum*.

In all cases positive for Histoplasma, primary pulmonary foci were present. In 4 of the human cases, more than one primary focus was found; and in 13 of the dogs, multiple primary foci were present. In some instances, canine primary pulmonary histoplasmosis resembled the epidemic type of the disease in man.

All of the cases in the humans except one showed involvement of the lymph nodes draining the primary focus. Nine dogs did not have demonstrable involvement of the lymph nodes corresponding to the primary focus.

Splenic calcifications were found in more than 60 per cent of the positive human cases; a few patients also showed hepatic calcifications. The spleens of the dogs were never involved.

Careful anatomic study of the healed or healing lesions in dog and man has been helpful in clarifying the pathogenesis. In 2 cases, lesions from possible exogenous reinfection are described. In an area as highly endemic as Cincinnati, exogenous reinfection can be anticipated, the Eden Park watertower incident being an example (21, 22). Infection during adult life in the endemic area is a regular occurrence. In the long run, no adult immigrant escapes infection. The adult primary complex has little tendency to calcify. The histoplasmoma in many cases represents a large primary lesion acquired during adult life. It is a manifestation of the disease seen more often outside than inside the endemic area, and more often in immigrants than in natives within the endemic area. Cavitary histoplasmosis, on the other hand, is very much confined to the endemic area. It is a late manifestation of the disease and in some cases may be the result of exogenous reinfection.

Sumario

Histopatología General de la Histoplasmosis Humana y Canina

En 55 autopsias consecutivas ejecutadas en la ciudad de Cincinati, Ohio, en enfermos adultos, que habían tenido dolencias distintas de la histoplasmosis activa, se descubrió histoplasmosis primaria curada en 47 (85 por ciento). En 20 (20 por ciento) de 100 perros procedentes de la zona de Cincinati, se encontraron lesiones de histoplasmosis primaria cicatrizadas o en vías de cicatrización.

Las radiografías de los pulmones y los bazos resultaron útiles para descubrir las lesiones. En todos los casos, se diagnosticó microscópicamente la naturaleza histoplásmica de las lesiones a base de la presencia de microbios de las dimensiones, forma y propiedades tintoriales del *Histoplasma capsulatum*.

En todos los casos positivos para *Histoplasma*, había focos pulmonares primarios. En 4 de los

casos humanos, se observó más de un foco primario, y en 13 de los perros existían focos primarios múltiples. En algunos casos, la histoplasmosis pulmonar primaria canina semejaba la forma epidémica de la enfermedad en el hombre.

Todos los enfermos humanos, menos uno, revelaban invasión de los ganglios linfáticos que drenaban el foco primario. Nueve perros no tenían invasión observable de los ganglios linfáticos que correspondían al foco primario.

Se observaron calcificaciones esplénicas en más de 60 por ciento de los enfermos humanos "positivos"; algunos también mostraban calcificaciones hepáticas. Los bazos de los perros no se afectaron nunca.

El cuidadoso estudio anatómico de las lesiones curada o en curación en el perro y el hombre resultó útil para esclarecer la patogenia. En 2 casos, se describen lesiones debidas a posible reinfección exógena. En una zona tan endémica como la de Cincinati, cabe esperar reinfección exógena, ofreciendo ejemplo de ello el incidente observado en la torre de agua del Parque Edén (21, 22). La infección durante la vida adulta en la zona endémica es un acontecimiento ordinario. A la larga, ningún inmigrante adulto escapa la infección. El complejo primario adulto muestra poca tendencia a la calcificación. En muchos casos, el histoplasmoma representa una lesión primaria grande adquirida durante la vida adulta, siendo una manifestación de la enfermedad observada más a menudo fuera que dentro de la zona endémica, y más a menudo en los inmigrantes que en los naturales en la zona endémica. Por otro lado, la histoplasmosis cavitaria se encuentra muy limitada a la zona endémica. Manifestación tardía de la dolencia, puede en algunos casos ser la consecuencia de una reinfección exógena.

Resume

Pathologie générale de l'histoplasmose humaine et canine

Les auteurs ont trouvé une histoplasmose primaire guérie, chez 47 (85%) de 55 autopsies consécutives, pratiqées à Cincinnati, Ohio, sur des malades adultes qui eurent des maladies autres qu'une histoplasmose active. Ils trouvèrent des lésions d'histoplasmose primaire guéries ou en voie de guérison, chez 20 (20%) de 100 chiens de la région de Cincinnati.

Des radiographies des poumons et des rates s'avérèrent utiles pour démontrer les lésions. La nature histoplasmique des lésions fut diagnostiquée dans tous les cas par le microscope, en se basant sur la présence d'organismes de la taille, de la forme et ayant les propriétés de coloration d'*Histoplasma capsulatum*.

Dans tous les cas positifs d'Histoplasma, il y eut des foyers primaires pulmonaires. Dans 4 des cas humains, on trouva plus d'un foyer primaire, et chez 13 chiens, il y avait de multiples foyers primaires. Dans quelques cas, l'histoplasmose primaire pulmonaire du chien ressembla au type épidémique de la maladie chez l'homme.

Tous les malades humains, excepté un, montrèrent un envahissement des ganglions lymphatiques drainant le foyer primaire. Neuf chiens n'eurent pas d'envahissement démontrable des ganglions correspondant au foyer primaire.

Des calcifications spléniques furent trouvées chez plus de 60% des malades humains "positifs"; quelques malades montrèrent aussi des calcifications hépatiques. Les rates des chiens ne furent jamais envahies.

Une étude anatomique soigneuse des lésions guéries ou en voie de guérison chez le chien et l'homme a été utile pour clarifier la pathogénie. Dans 2 cas, les auteurs décrivent des lésions pouvant provenir d'une réinfection exogène. Dans une région aussi endémique que Cincinnati, on peut prévoir une réinfection exogène, l'incident du chateau d'eau d'Eden Park en étant exemple (21, 22). L'infection au cours de la vie d'adulte dans cette région endémique est d'une fréquence commune. A la longue, aucun immigrant m'échappe à l'infection. Le complexe primaire de l'adulte a peu de tendance à la calcification. L'histoplasmose dans beaucoup de cas représente une large lésion primaire acquise durant la période adulte de la vie. C'est une manifestation de la maladie vue le plus souvent à l'extérieur qu'à l'intérieur de la région endémique, et, plus souvent chez les immigrants que chez les indigènes de la région endémique. L'histoplasmose cavitaire, d'un autre coté, est surtout réduite à la région endémique. C'est une manifestation tardive de la maladie et elle peut être dans certains cas le résultat d'une réinfection exogène.

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ATTITUDES TOWARD SELF AND OTHERS IN THE SANATORIUM[1,2]

Alcoholic and Nonalcoholic Patients

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INTRODUCTION

The present study grew out of a larger investigation of the relationship between alcoholism and tuberculosis and of the behavior of alcoholic and nonalcoholic tuberculous patients during hospitalization. The earlier research indicated that the behavior of the patient while in the hospital appeared to be as much a function of his interaction with other patients and with the staff as of his individual social and psychologic pre-hospitalization dynamics (1–4).

This paper examines the hypothesis that alcoholic tuberculous patients can be differentiated from nonalcoholic tuberculous patients by their attitudes toward themselves, toward others, and toward social values, and by patterned interrelationships between these variables.

METHODS

Subjects: The two groups of experimental subjects had been hospitalized for more than two months. The first group consisted of 35 male tuberculous patients who had been diagnosed also as alcoholics.[3] The second group consisted of 32 male tuberculous patients who had no record of alcoholism. Both experimental groups were structured so as to contain Skid Row and non-Skid Row patients, so that the findings would not be contaminated by social class factors.

A control group of 32 nonalcoholic and nontuberculous subjects, of age, educational, and socio-economic status comparable with those of the patient groups, was also examined. The normal control group was studied so that, if it could be demonstrated that there were differences between alcoholic and nonalcoholic tuberculous patients' response patterns, it might be possible to indicate whether the attitudes of one group of subjects were more grossly deviant from the "normal" than the other.

Procedures: The instruments chosen were the LaForge and Suczek Interpersonal Checklist (6) and the Cornell Medical Index (7).

The Interpersonal Checklist (hereinafter referred to as ICL) consists of 128 adjectives and phrases descriptive of interpersonal behavior. The items are evenly distributed between eight test subsections, each of which samples a different aspect of interpersonal behavior. Each patient classified each behavioral item on a nine-point scale which ranged from "extremely favorable" to "extremely unfavorable." Next, he classified each item into the categories "Most people are" and "Most people are not." Finally, he described "I am" and "I am not."

The Cornell Medical Index Health Questionnaire (hereinafter referred to as CMI) consists of 195 items descriptive of physical and emotional symptoms. It elicits the attitudes of the patient toward his health.

Data analysis: The results of ten separate analyses which yielded significant differentiation between the groups being studied have been summarized in table 1 in order to permit simultaneous inspection of the components of each group's pattern of responses. Descriptive details of the different methods of data analysis are provided here as a necessary preliminary to the summary table. Each numbered heading corresponds to a numbered entry under the heading *Test Patterns* in table 1.

Interpersonal Checklist

1. Over-all group consensus: The first stage of the analysis was to assess the extent of homogeneity of response within each group. Each response protocol was converted into a profile by counting the number of items subscribed to in each of the eight test subsections, and then ranking the sections from most heavily endorsed to least heavily endorsed. The rank pattern of each protocol was then directly comparable with the rank pattern of all other protocols by methods of rank-order correlation. Kendall's *Coefficient of Concordance* (8), represented by the symbol W, was selected as the measure of amount of agreement or commonality of judgments between the subjects in each experimental group. This measure can vary from 0.00 (no agreement) to 1.00 (complete agreement).

The rank pattern which is referred to as *ideal* represents the pattern of all items which the subject classified as being favorable to any degree.

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[2] This study has been supported in part by a Senior Research Fellowship (SF 262) from the U. S. Public Health Service, and by Firland Research Fund.

[3] The criteria for categorizing patients as alcoholics or as nonalcoholics were the responses of the patients to the Scale of Preoccupation with Alcohol (5).

2. Average correlation between self-description and high conformity pattern: When there was an outstanding amount of agreement within groups, the agreement tended to be on a pattern of self-description which claimed conformity as its most prominent characteristic. This pattern, labeled the "high conformity pattern," is expressed by the ranking of the ICL octants in the following order from most to least important: cooperative-overconventional, responsible-overgenerous, docile-dependent, competitive-exploitive, blunt-aggressive, modest-self effacing, managerial-autocratic, and skeptical-distrustful.

When the rank order of each individual's self-description had been correlated with the high conformity pattern, the correlations for each group of subjects were averaged by use of the z' transformation.

3. Occurrence of 15 ingratiating-placating items in self-description: Subjects who saw themselves as being essentially conforming tended to ascribe to themselves the following fifteen traits which are focused on social acceptance and on getting along well with others: *apologetic, usually gives in, admires and imitates others, always pleasant and agreeable, often admired, sociable and neighborly, tender and soft-hearted, gives freely of self, too easily influenced by friends, generous to a fault, wants everyone's love, friendly all the time, too lenient with others, tries to comfort everyone,* and *too willing to give to others.* Count was made of the number of these traits occurring in the self-description of each individual.

4. Average correlation between self-description and most people: Each individual's rank pattern of self-description was correlated with his description of most people, and the correlations obtained within each group of subjects were averaged.

5. Difference between self and most people, 9 selected items: Nine traits were selected on which controls tended to emphasize their difference from most people. These include: I am, but most people are not: *self-confident, straightforward and direct, stubborn, hardly ever talks back.* I am not, but most people are: *lacks self-confidence, boastful, proud and self-satisfied, lets others make decisions,* and *likes to be taken care of.* Count was made of the number of these trait differences occurring in each individual's record.

6. Unfavorable value comparisons between self and most people: The average social desirability value of the traits by which the individual described himself within each octant was compared with the average value of the traits by which he described most people within the same octant. Count was made of the number of octants in which each subject perceived his own traits as having no greater value than the traits displayed by most people.

7. Deviant social desirability values, 17 items: All patient groups in the tuberculosis hospital tended to attach different values to certain of the ICL items than did the controls. Patients were more likely to consider as favorable: *able to give orders, able to doubt others, very anxious to be approved of, outspoken,* and *forceful*; and as unfavorable: *can be indifferent to others, usually gives in, likes everybody,* and *spoils people with kindness.* They were more likely to use the extreme scale points for categorizing *affectionate and understanding* and *considerate* as being favorable; similarly, they stressed the unfavorableness of *touchy and easily hurt, easily led, always giving advice, impatient with others' mistakes,* and *will confide in anyone.* Finally, the patient groups were more likely to think of the trait *dependent* as either extremely favorable or extremely unfavorable. Count was made of the total number of these 17 items to which each subject had assigned a social desirability value which deviated in the described way.

Cornell Medical Index

8. Total score: Each individual's total number of "yes" responses to the CMI was counted.

9. Neurotic index score: The CMI contains means of evaluating medically significant emotional disturbance (6, page 7). Each subject's questionnaire was classified as having or as not having any indication of emotional disturbance.

10. Score on items differentiating between alcoholic and nonalcoholic tuberculous patients: In previous research on alcoholic and nonalcoholic tuberculous patients (8), it was found that 28 items differentiated between the two groups.[4] Each of the differentiating items had been assigned a weight determined by the size of the critical ratio of the differences between the two groups. Each subject's CMI was scored on these items and the distribution of scores for the three groups were combined and divided into quartiles.

Results

In table 1 the results of the 10 measures which have been described are tabulated in parallel columns for the three groups of subjects. Several patterns of response are clearly evident.

In the first three test patterns, the alcoholic patients were indistinguishable from the controls, and the nonalcoholic patients displayed significantly deviant patterns. Alcoholic patients and controls showed even and consistent amounts of agreement in all of their judgments. They saw themselves as having a pattern of traits which is essentially conforming and as having many of the characteristics which lead to easy social interaction and acceptance.

The nonalcoholic patients had little agreement on what they or others were like and tended to see themselves and others in a wide variety of

[4] The items are 11, 22, 24, 29, 33, 35, 38, 41, 43, 57, 58, 64, 66, 70, 71, 72, 81, 83, 86, 88, 123, 128, 136, 139, 177, 178, 187, and 195.

TABLE 1

COMPARISON OF TUBERCULOUS ALCOHOLICS, TUBERCULOUS NONALCOHOLICS, AND CONTROLS ON INTERPERSONAL CHECKLIST (ICL) AND CORNELL MEDICAL INDEX (CMI) PATTERNS

Test Patterns	Subjects			Significance of Differences
	Tuberculous Alcoholics	Tuberculous Nonalcoholics	Controls	
1. ICL: Over-all group consensus*				No method exists for comparing W's†
a. Self	0.43	0.17	0.46	
b. Most people	0.48	0.25	0.45	
c. Ideal	0.51	0.65	0.49	
2. ICL: Average correlation between between self-description and high conformity pattern	0.71	0.52	0.74	Differences between tuberculous nonalcoholics and each other group significant at 0.01 level
3. ICL: Occurrence of 15 ingratiating-placating items in self-description				Differences between tuberculous nonalcoholics and each other group significant at 0.01 level
7 or more	30	15	25	
6 or less	5	17	7	
4. ICL: Average correlation between self-description and most people	0.72	0.52	0.59	Differences between tuberculous alcoholics and each other group significant at 0.01 level
5. ICL: Difference between self and most people, 9 selected items				Difference between tuberculous alcoholics and tuberculous nonalcoholics significant at 0.02 level; differences between controls and each other group not significant
2 or more	15	23	16	
1 or less	20	9	16	
6. ICL: Unfavorable value comparisons between self and most people				Differences between tuberculous alcoholics and each other group significant at 0.02 level
3 or more subsections	29	18	15	
2 or less subsections	6	14	17	
7. ICL: Deviant social desirability values, 17 items				Differences between controls and each other group significant at 0.01 level
8 or more	26	24	7	
7 or less	9	8	25	
8. CMI: Total score				Differences between groups significant at 0.01 level
30+	14	5	0	
20–29	5	6	7	
10–19	10	14	8	
0–9	3	4	15	
Totals‡	32	29	30	
9. CMI: Neurotic index score				Differences between tuberculous alcoholics and controls significant at 0.05 level
1 or more indications of emotional disturbance	22	17	14	
No indication of emotional disturbance	10	12	16	
10. CMI: Score on items differentiating between alcoholic and nonalcoholic tuberculous patients				Differences between tuberculous alcoholics and tuberculous nonalcoholics significant at 0.05 level; differences between tuberculous alcoholics and controls significant at 0.01 level
Quartile 4, score 15+	15	6	2	
Quartile 3, score 9–14	8	9	4	
Quartile 2, score 6–8	6	4	11	
Quartile 1, score 0–5	3	10	13	

* All W's significant at 0.01 level.

† $W = \frac{\text{sum of squares between columns}}{\text{total sum of squares}}$.

‡ Totals are smaller than in previous sections of tables as 3 alcoholics, 3 nonalcoholics, and 2 controls did not complete CMI.

ways. However, as a group, they agreed highly on the values to be placed on the behavior and attitudes tapped by the Interpersonal Checklist, and demonstrated that they had at least as uniform a frame of reference as the other subject groups. Despite their low over-all agreement, the nonalcoholic patients showed high agreement on certain items. They were much more likely than the controls to attribute to themselves such undesirable traits as being *sarcastic* or *passive and unaggressive* or *stubborn* and to see themselves as lacking the qualities of being *able to criticize self, accepts advice readily, trusting and eager to please, enjoys taking care of others, friendly all the time,* and *loves everyone.* Thus, they more frequently attributed to themselves certain undesirable qualities and omitted from their self-descriptions certain desirable forms of behavior. The alcoholic patients were differentiated from the nonalcoholic patients by presenting the same pattern on these items as the controls. They saw themselves as differing from the controls only in that they attributed the following qualities to themselves: *can be indifferent to others, resents being bossed, often helped by others,* and *too easily influenced by friends.* The nonalcoholic patients saw themselves as being less conventional and less conforming than did either the controls or the alcoholic patients. They did not describe themselves as placing much emphasis on getting along well with others in an ingratiating way, while this was important to both the alcoholic patients and to the controls.

In test pattern 4, it was the alcoholic patients, rather than the nonalcoholics, who exhibited deviant responses. The alcoholic patients claimed to be much more like most people than did either the nonalcoholic patients or the controls. The alcoholic patients admitted to significantly fewer of the specific differences itemized in test pattern 5 than did the nonalcoholic patients.

The data up to this point have highlighted different facets of the observation that the nonalcoholic patients tend to exhibit self-concepts which include a lack of group conformity and feelings of being different and isolated from most people, especially with respect to getting along easily with others. The patient who is also alcoholic appears to overcome or to deny these feelings of difference and to present a picture which is indistinguishable in most dimensions from that of the controls.

On the basis of research findings on other samples of alcoholic and nonalcoholic patients (9), it was hypothesized that the alcoholic tuberculous patient is denying reality in seeing himself as being no different from others. In other words, his perceptions represent a facade.[5]

Test pattern 6 again showed the alcoholic patients to be different from both nonalcoholic patients and controls in their tendency to see their own traits as less desirable than those of others, despite their strong claims that they are like others. It appeared that the controls thought that they met their own values and standards satisfactorily. The scores of the nonalcoholic patients were like those of the controls with respect to over-all self-evaluation and degree of similarity to most people, and may reflect acceptance of their feelings of being different in contrast to apparent denial of the alcoholic.

The values attributed to certain checklist items discriminate both patient groups from control subjects. These data would support the impression that the thinking and attitudes of the alcoholic patients are not as unchanged by their illness and hospitalization as they would like to have it appear. The hypothesis that the conforming patterns which they display are, indeed, a facade is apparently tenable.

The total number of "yes" responses to the Cornell Medical Index provides a measure of the individual's perception of his emotional and physical health. The three groups differed significantly as to total scores. The controls considered themselves to be relatively symptom free, the nonalcoholic patients had a moderate number of symptoms, while the alcoholic patients clustered in the very high symptom categories. Both patient groups differed significantly from

[5] When alcoholics, on the basis of their physicians' judgments, were assigned to the categories of far advanced, moderately advanced, and minimal tuberculosis and their CMI responses were analyzed, it was found that total CMI scores were inversely related to the extent of tuberculosis. The nonalcoholic tuberculous patients responded as expected, with total scores positively related to the physicians' judgments of the extent of the disease. Thus, it would appear that the nonalcoholic tuberculous patients rather correctly assessed the extent of their illness, whereas the alcoholics' pattern indicated that the sicker they were clinically, the nearer to normal they presented themselves as being (9).

TABLE 2
CONSISTENCY OF PATTERN AND RELATION TO DIAGNOSIS

Relation to Diagnosis	Degree of Consistency			
	Marked (5 or 6 measures of same type)	Moderate (4 measures of same type)	Equivocal (3 measures of each type)	Total
Correct identification	31 (50.8%)	7 (11.5%)		38 (62.3%)
Incorrect identification	9 (14.8%)	6 (9.8%)		15 (24.6%)
Impossible to identify			8 (13.1%)	
Total	40 (65.6%)	13 (21.3%)		

the controls,[6] but not from each other.[7] The data again support the hypothesis that the tuberculous alcoholics, in maintaining that they are exactly like the controls, are erecting a facade.

Six measures separated alcoholic patients as a group from nonalcoholic patients. Specifically, these measures are: the correlation of self-description with the high conformity pattern (0.71 or greater); seven or more ingratiating and placating traits in the self-description; correlation of self-description and most people (0.71 or greater); "I am different from most people" on selected items; unfavorable comparison of self traits with most peoples' traits; and score on differentiating items from the Cornell Medical Index.

The final question is: Does each subject tend to exhibit only a few of the differentiating characteristics, or does the occurrence of one characteristic pattern imply that the others are also more likely to occur in the same response record?

Both the consistency of pattern of the response records and the relationship between pattern and actual diagnosis are presented in table 2. Each test measure can be designated as "alcoholic-like" or "nonalcoholic-like" according to which group of patients tended to give that type of response more frequently. Two or more measures are considered consistent when they reflect the same type of response.

[6] P, 0.01 and 0.05, respectively.

[7] In previous research, using the CMI over a four-year period, the alcoholic tuberculous patients tended to show significantly more symptoms than did the nonalcoholic tuberculous patients (9).

These findings indicate that individual response records display marked consistency in almost two of three cases and some consistency in 87 per cent of the cases. It is apparent also that some subjects display consistent patterns which exhibit few or none of the characteristics common to their diagnostic group. In other words, the attitudes sampled appear to represent a "symptom-complex" whose differentiation is highly significant on a group basis, but which can be used to identify individuals correctly as to diagnosis in only 62 per cent of the cases.

DISCUSSION

The present study found measurable differences between alcoholic and nonalcoholic tuberculous patients who had been hospitalized for two months or longer. The differences lay in their attitudes toward themselves, in their perceptions of others, and in their relationships to others and to social values. The nonalcoholic tuberculous patients' constellation of attitudes indicated that they lacked an awareness of what their own role was and of what the roles of others were. They felt different from other people, isolated from them, and dissatisfied with themselves. At the same time, they seemed to have some acceptance of these feelings. In their perceptions of their state of health, they appeared to be realistic. In contrast, alcoholic patients denied any differences between themselves and others and shared with other alcoholic patients a view of their own role and that of others as being essentially alike and normal. It was possible to demonstrate that these attitudes represented a denial of underlying feelings of being undesirable.

The study indicated neither the source of these attitude clusters nor their relationship to alcoholism and to tuberculosis. Therefore, the possible implications for theory and for patient management can only be tentatively explored.

In the literature there are three hypotheses which might account for the present findings. They are not mutually exclusive, and it may be that each contributes some knowledge about the ways in which patients perceive their own roles and those of others.

1. These attitude clusters are antecedent to contracting tuberculosis and are etiologic in character, i.e., factors which lower host resistance to infection and to the spread of infection.

2. These attitudinal constellations represent responses to the diagnosis of a severe chronic illness which, even today, is culturally defined as stigmatizing.

3. The attitudes represent a product of the process of prolonged hospitalization in a highly specialized institutional setting.

The first hypothesis is derived from the literature on the psychosomatic aspects of tuberculosis. There is a school of thought which holds that clinically detectable tuberculosis is a function of the virulence of the organism, the amount of exposure, and the psychologic and physical state of the host. While there is little agreement on the specific personality constellations which accompany vulnerability to tuberculosis, all would agree that the characteristics which they consider important would leave the host feeling inadequate, isolated, and unclear about himself and about his relationship to others. Such a school of thought would hold that the attitudinal constellations found in this study were etiologic agents in the onset of clinically active tuberculosis (10).

The data on which this theory rests were gathered from patients who had clinically active tuberculosis and who had been hospitalized for unspecified lengths of time. Until such time as it is possible to study people prior to infection, it will be impossible to test such an hypothesis adequately. Even if the data were gathered immediately upon detection of tuberculosis, the impact of the diagnosis would have to be evaluated.

If such attitudes are etiologic factors, it would be anticipated that alcoholic and nonalcoholic patients would share them. In this study this was not the case. On the contrary, these attitudes differentiated between alcoholics and nonalcoholics, both of whom suffered from tuberculosis. Such findings cast doubt on the etiologic hypothesis. However, the possibility remains that alcoholics and nonalcoholics arrive at clinically detectable tuberculosis by way of different psychologic routes.

The second hypothesis, that these attitudes result from the diagnosis of tuberculosis, also has some support in the literature on tuberculosis and in the response to serious incapacitating illness. Both Wittkower (11) and Derner (12) point out that the response to diagnosis is far from unitary and is determined by the way in which the diagnosis is presented to the patient, the patient's personality and experience, and the patient's definition of what the illness means to him. Common patterns in responding to the diagnosis of serious, incapacitating illness are: denial, and feelings of isolation and unworthiness, of being personally less worth while due to the pathology of a part of one's physical makeup.

The present data suggest that alcoholic patients respond with denial while nonalcoholic patients respond by feelings of isolation, of being different, and of falling short of their own ideals. The latter, through the diagnosis, lose their usual frame of reference for viewing their world and where they and others fit into it. Tyhurst and his associates (13) consider this type of response to be the normal, but transient, reaction in a crisis or disaster situation in which the person's usual patterns of behavior become inoperative.

The third hypothesis, that the attitudes are, in part, the products of hospitalization, also has some support in the literature. Roth (14) discusses the evolution of the role of the tuberculous patient and the changes in roles as hospitalization proceeds, as does Seidenfeld (15). Stanton and Schwartz (16) and Caudill (17) discuss the ways in which the roles of mentally ill patients are learned from staff and other patients. Jackson's studies of tuberculous alcoholics point out the factors in the sanatorium setting which contribute to a specific type of role definition for alcoholic tuberculous patients (1). Against this hypothesis are the works of Muldoon (18), Charen (19), and Berger (20). The first two found no changes due to the length of hospitalization, and the third found only transient

changes. However, these writers were studying basic personality characteristics which, theoretically, would not be influenced as much by hospitalization or diagnosis as would role conceptions.

Realistically, a person who is hospitalized for tuberculosis *is* different from most other people and must make changes in his concepts of his roles and those of others. New roles take time to evolve and to become integrated into a self-concept which has been altered to accord with the new reality. It also takes time for the tuberculous patient to learn and to integrate what he can expect. It may be that the nonalcoholic patient's customary sense of himself and of other people and of the relationship of others to him has been shaken by his illness to a greater extent than that of the alcoholic patient and that it takes longer to become integrated into a new and stable pattern.

From what is known about alcoholic and nonalcoholic patients prior to hospitalization, some support can be gained for this interpretation. The alcoholic patient has been relinquishing socially approved adult roles over a long period of time and has made gradual adaptations to being different from others. Hospitalization and tuberculosis bring about another change, but the alcoholic has well-established techniques to mobilize. These adaptive techniques tend to be shared by other alcoholics, based as they are, in part, upon their common experiences (2, 4).

For the nonalcoholic, the diagnosis of tuberculosis—an illness which has lingering socially undesirable attributes, which requires isolation from well people, which is treated by people in masks—raises realistic barriers to the maintenance of the pre-hospitalization self-concept and requires quantitatively and qualitatively greater change. Nonalcoholic tuberculous patients have had no particular uniformity of prior experience, no common adaptive techniques. It would not be surprising, therefore, that they should see themselves in a variety of ways and have no shared frame of reference for describing themselves and other people; that they should feel isolated, different, and uncertain about where they fit.

The attitudes of the alcoholic patients inevitably lead to an impasse in communication with other people. Insofar as an ability to perceive oneself and others realistically is a prerequisite to successful adaptation and to meaningful communications, the attitudes of the alcoholic defeat his attempts to adapt and to communicate. In a setting in which the general public, other patients, and the staff hold a stereotype of the alcoholic as different and as deviant, the alcoholic patients' insistence on their similarities to others and on their normality leads to dysfunctional and disturbing interactions. They tend to attribute to others erroneously their own motivations, perceptions of situations, and meanings. In an earlier research report (1) the types of difficulties which ensue were described. When the hospital staff is aware of the assumptions on which the alcoholic patient operates, it is able to understand him better and does not become involved as frequently in situations which it interprets as problems.

Insofar as the feelings of the nonalcoholic patients derive from cultural attitudes toward tuberculosis as stigmatizing, health education efforts and open discussion might be useful. The patients could be helped to clarify the implications which the illness has for their future roles and future relationships with others.

Tyhurst (13) suggests that the patient who is in crisis can be helped by those who are aware of the process he has gone through, to integrate the past and the crisis with the present and the future. Acceptance and understanding of his feelings are important in helping him to see these feelings in the rational context of what has happened. Supportive ritual and the use of the hospital as a "transitional community" to help the person to become integrated into the environment beyond the sanatorium on discharge can shorten the period of discontinuity and permit the patient to achieve a new integration. Regardless of which hypothesis accounts for the attitudes of the nonalcoholic tuberculous patient, some remedial action appears to be called for.

Summary

The LaForge and Suczek Interpersonal Checklist and the Cornell Medical Index were used to evaluate the ways in which 35 alcoholic and 32 nonalcoholic male tuberculous patients differed in their attitudes toward themselves, others, and the ideal. Thirty-two nonalcoholic, nontuberculous, nonhospitalized subjects served as controls.

The nonalcoholic tuberculous patients' attitudes indicated that they lacked an awareness of their own role and that of others. They felt different from other people, isolated from them,

and dissatisfied with themselves. At the same time, they seemed to have some acceptance of these feelings. In their perceptions of their state of health, they appeared to be realistic. In contrast, alcoholic patients denied any differences between themselves and others, and shared with other alcoholic patients a view of their own role and that of others as being essentially alike and normal. It was possible to demonstrate that these feelings represented a facade—a denial of underlying feelings of being undesirable. It was demonstrated that the attitudes represented "a symptom complex" whose differentiation was highly significant on a group basis, but which could be used to identify individuals correctly in only 62 per cent of the cases.

Sumario

Actitudes hacia Sí Propios y hacia Otros en el Sanatorio: Los Enfermos Alcohólicos y No Alcohólicos

Se usaron la Lista Comprobadora Interpersonal de LaForge y Suczek y el Indice Médico de Cornell para diferenciar los modos en que 35 tuberculosos alcohólicos y 32 no alcohólicos discrepaban en sus actitudes hacia sí propios y hacia otros, y lo ideal. Sirvieron de testigos 32 sujetos que no eran alcohólicos ni tuberculosos y no estaban hospitalizados.

Las actitudes de los tuberculosos no alcohólicos indicaban que no tenían idea de su propio papel ni del de los otros. Se sentían distintos de los demás, aislados de éstos, y descontentos con sí propios. Al mismo tiempo, parecía que habían aceptado algunos de estos sentimientos. En la percepción de su estado de salud, parecían realistas. En contraposición, los alcohólicos negaban que hubiese la menor diferencia entre ellos y los demás y compartían con otros alcohólicos la opinión de que su propio papel y el de los demás eran en el fondo semejantes y normales. Era posible demostrar que estos sentimientos representan una fachada—la negación de que abrigaran ideas ocultas de no ser bienvenidos. Se demostró que esas actitudes representan un "complejo sintomático," cuya diferenciación era sumamente importante para el grupo en conjunto, pero que no podía usarse para identificar correctamente a los individuos más que en 62 por ciento de los casos.

Resume

Attitudes vis à vis d'eux-mêmes et des autres en sanatorium: malades alcooliques et non alcooliques

Les auteurs utilisèrent la "liste de contrôle interpersonnelle de Laforge et Suczeck" et "l'index médical de Cornell" pour évaluer les façons dont 35 malades mâles tuberculeux alcooliques et 32 non alcooliques diffèrent dans leurs attitudes vis à vis d'eux-mêmes, des autres, et de leur idéal. Trente deux des sujets, non alcooliques, non tuberculeux, non hospitalisés servirent d'éléments de comparaison.

Les attitudes des tuberculeux non alcooliques indiquèrent qu'ils manquent du sens de leur propre rôle et de celui des autres. Ils se sentaient différents des autres gens, isolés d'eux et insatisfaits d'eux-mêmes. En même temps, ils semblèrent avoir quelqu'acceptation de ces sentiments. Dans leur perception de leur état de santé, ils apparurent réalistes. Au contraire, les malades alcooliques nièrent toute différence entre eux et les autres, et partagèrent avec d'autres malades alcooliques le point de vue de leur propre rôle et celui des autres, se sentant semblables et normaux. Il fut possible de démontrer que ces sentiments représentent une façade—une négation des sentiments sous-jacents d'être indésirables. Il fut montré que ces attitudes représentent un "symptôme-complexe" dont la différenciation fut très nette en se basant sur l'étude d'un groupe, mais qui ne put être utilisée, pour caractériser correctement des individus, que dans 62% des cas.

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Case Reports

SPONTANEOUS PNEUMOTHORAX DURING STEROID THERAPY OF RAPIDLY PROGRESSIVE, FAR ADVANCED PULMONARY TUBERCULOSIS[1]

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Introduction

Although spontaneous pneumothorax was previously not uncommon in rapidly progressive pulmonary tuberculosis, this has not been the experience of the present writers in recent years with modern chemotherapy. Two cases, reported below, are of interest in that respect and also in that they may possibly represent a complication of steroid therapy in rapidly progressive, far advanced, pulmonary tuberculosis.

Case Reports

Case 1 (N. B.). A 24-year-old Latin-American laborer was admitted to the Colorado General Hospital on March 6, 1958, complaining of cough and pleuritic pain of two weeks' duration. Nine months prior to admission, he first noted the onset of cough and fever. He was treated with penicillin by his private physician; his symptoms abated slightly. Three months prior to admission, his cough became productive of blood-streaked sputum and was accompanied by chills, fever, sweats, dyspnea on exertion, weakness, and the loss of 45 pounds.

Inquiry into the past and family history was noncontributory. Physical examination revealed a blood pressure of 95 systolic, 60 diastolic in mm. of mercury. His pulse was 140 per minute; respiration, 36 per minute; and temperature, 38.6°C. The patient appeared both cachectic and acutely ill. Dullness, decreased breath sounds, and rales were noted over the right lower lung field, and rales over the right anterior chest. Dullness and bronchial breath sounds were heard over the entire left upper chest. Rales were heard over the left lower lung field.

Laboratory examination: The hemoglobin was 10 gm.; leukocytes were 9,800 per cu. mm. with a left shift; and urinalysis was negative. A 5-TU dose of PPD revealed 9 mm. of induration at forty-eight hours. Sputum showed many acid-fast bacilli on microscopy, and culture revealed typical *M. tuberculosis*, catalase positive, and fully susceptible to isoniazid, para-aminosalicylic acid (PAS), and streptomycin. The chest roentgenograms are presented in figure 1.

On March 6, 1958, the patient began receiving isoniazid (600 mg.), sodium PAS (12 gm.), and pyridoxine (100 mg.) all by mouth, and streptomycin (1 gm.) intramuscularly, each daily. Because of the hypotension and severe clinical toxicity, prednisone therapy (30 mg. per day) was started on March 7, 1959. The clinical response to prednisone was prompt and dramatic.

On March 19, 1958, the patient suddenly complained of severe left-sided pleuritic chest pain and intense dyspnea. Left-sided pneumothorax was readily discerned by physical findings and chest roentgenograms. He was treated with an indwelling chest catheter leading to an underwater seal. During the ensuing three weeks, the patient had repeated episodes of spontaneous pneumothorax: on both sides on March 31, 1958, on the right side on April 5, 1958, and again on the left side on April 9, 1958. These were each treated in the same fashion. Thereafter, coincident with cessation of prednisone therapy, he showed gradual, steady improvement without recurrence of pneumothorax. Pneumothorax has not recurred through November, 1959.

Case 2 (A. P.). A 26-year-old Latin-American housewife was admitted to the Colorado General Hospital on November 1, 1958, complaining of cough and weight loss of four months' duration. In March, 1958, she had a routine chest roentgenogram which was negative except for a Ghon complex on the left. At this time she had noted a swelling in the left side of her neck which was incised and drained by her private physician. The drainage continued for eight months until her admission. Four months prior to admission, she noted the onset of cough, fever, sweats, dyspnea on exertion, and intermittent right pleuritic chest pain. She also lost 20 pounds. The patient had been treated with radioactive iodine in July, 1957, for hyperthyroidism; thereafter this condition was well controlled on 60 mg. of thyroid extract a day. Social and past histories were otherwise noncontributory.

Physical examination revealed a blood pressure of 100 systolic, 70 diastolic in mm. of mercury; pulse, 120 per minute; respiration, 36 per minute; and temperature, 40° C. She appeared both

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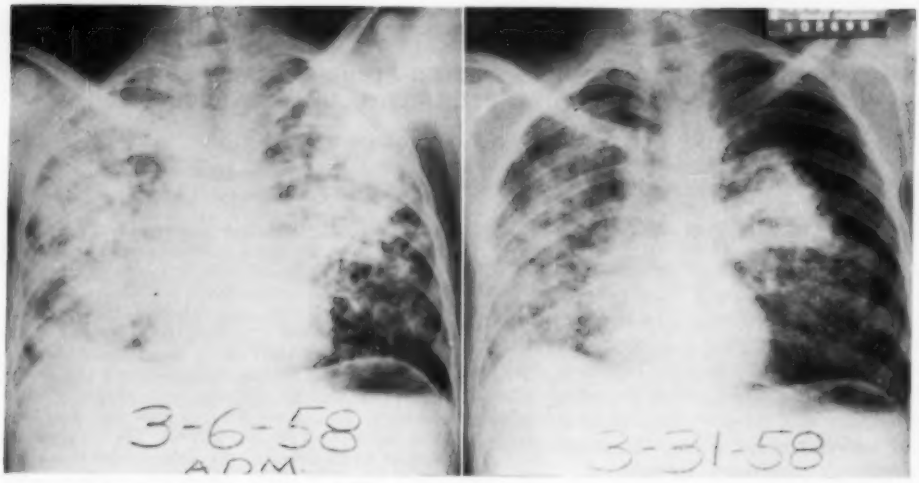

FIG. 1 (Left). Admission chest roentgenogram of *Case 1* (N. B.) showing extensive bilateral caseopneumonic tuberculosis.

(Right). Twenty-four days after starting antituberculous chemotherapy plus prednisone; film shows some clearing and pneumothorax bilaterally.

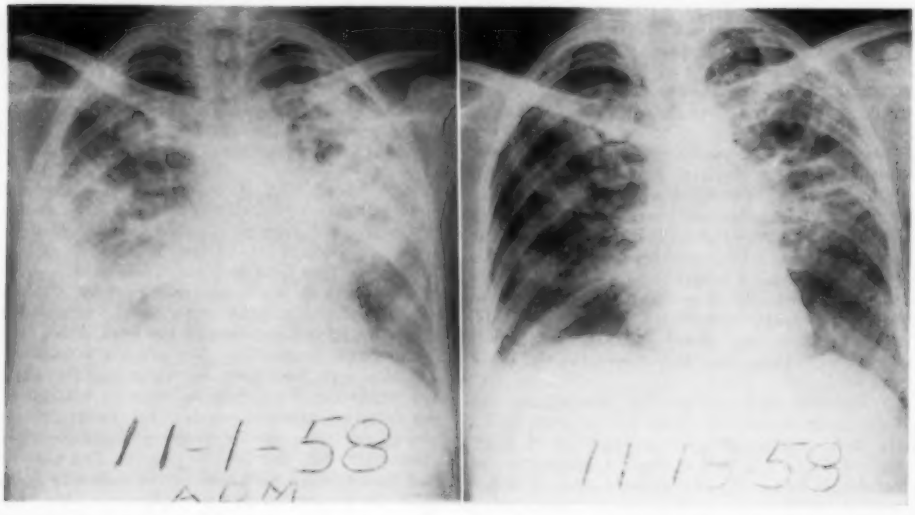

FIG. 2 (Left). Admission chest roentgenogram of *Case 2* (A. P.) showing extensive bilateral caseopneumonic tuberculosis, especially on the left with a right pleurisy with effusion.

(Right). Seventeen days after starting antituberculous chemotherapy plus prednisone; film shows some clearing bilaterally plus a right pneumothorax and spontaneous disappearance of fluid on the right.

acutely and chronically ill. The left cervical lymph nodes were swollen, firm, and matted together and to the underlying tissues. A small neck wound drained a small amount of thin mucopurulent material. Dullness and increased breath sounds were noted over both upper lobes. Rales were heard over the right lower lobe.

The hemoglobin was 10 gm.; leukocytes were 14,000 per cu. mm. with a left shift; and urinalysis showed pyuria. Urine culture grew *Streptococcus fecalis*; urine cultures for *M. tuberculosis* were negative. A 5-TU dose of PPD revealed 7 mm. of induration at forty-eight hours. Sputum revealed innumerable acid-fast bacilli on microscopy. Cultures revealed typical *M. tuberculosis* catalase positive, and fully susceptible to isoniazid, PAS, and streptomycin. Chest roentgenograms are shown in figure 2.

On November 1, 1958, the patient was placed on isoniazid (600 mg.), sodium PAS (12 gm.), pyridoxine (100 mg.), all by mouth, plus streptomycin (1 gm. intramuscularly) each daily. On November 5, 1958, because she continued to be markedly febrile and toxic, prednisone therapy (60 mg. a day) was started. This was followed by a dramatic clinical improvement, including return of the patient's temperature to normal range.

A routine chest film obtained on November 13, 1958, revealed a partial right pneumothorax and spontaneous disappearance of previously present fluid. No thoracentesis was performed, nor was there a history or observation of the patient's coughing up the fluid. The pneumothorax persisted until soon after cessation of prednisone therapy on December 15, 1958, but did not require aspiration or intubation. The patient's subsequent course was one of gradual, steady improvement without recurrence of pneumothorax through November, 1959.

Discussion

The literature concerning spontaneous pneumothorax in pulmonary tuberculosis has been reviewed. Before the era of chemotherapy, the overall incidence was reported as 0.73 to 3 per cent, 4 to 13 per cent occurring in fatal cases (1).

Since the advent of chemotherapy, little comment on this complication has appeared in the literature. The controversy continues over the frequency of tuberculosis as the etiology of spontaneous pneumothorax in otherwise "healthy" people (2–6).

In one series of 20 cases of pneumothorax occurring in tuberculosis during the years 1950 to 1954, no case was reported to have been treated with steroids; the majority of these were dissimilar from the cases reported here, not only in the circumstances under which pneumothorax appeared but also in the chemotherapy received (7). Among numerous studies of the use of steroids in the treatment of tuberculosis, none found have reported pneumothorax as a complication (8–10).

A case has been reported of a patient treated for leprosy with deltadihydrocortisone, 20 mg. a day for eight days; after this he was noted to have clinical, roentgenographic, and laboratory evidence of rapidly progressive pulmonary tuberculosis associated with spontaneous pneumothorax (11).

Thirty patients with spontaneous pneumothorax were admitted to Colorado General Hospital during the ten years 1948–1958: 4 of these had pulmonary tuberculosis and include the 2 reported here, one whose tuberculosis was inactive by all criteria, and one showing only minimal roentgenographic evidence of activity without bacteriologic confirmation.

From January, 1956, to January, 1959, 120 patients were admitted to the Colorado General Hospital with a diagnosis of far advanced, active pulmonary tuberculosis. Seven of these were treated with steroids (prednisone, 10–60 mg. a day for one to ten weeks). Two of these 7 cases (those reported here) were complicated by spontaneous pneumothorax. Three additional patients with miliary and meningeal tuberculosis were treated with steroids without this complication.

Spontaneous pneumothorax in active pulmonary tuberculosis is believed to be due to the progression of a subpleural caseous focus. Adrenocortical steroids inhibit the inflammatory process and are believed by some to inhibit the tendency to fibrosis; thus, it is plausible that spontaneous pneumothorax might occur when steroids are used to treat very extensive tuberculosis which is progressing too rapidly to be accompanied by much fibrosis.

During the same 3-year period, 12 patients with similar rapidly progressive, far advanced pulmonary tuberculosis were treated with the same chemotherapy regimen plus steroids at Denver General Hospital. Spontaneous pneumothorax occurred surely in one and probably in a second one of these 12 cases (12).

Summary

Two cases of spontaneous pneumothorax occurred among 7 patients with far advanced, rapidly progressive pulmonary tuberculosis who received adrenocortical steroids together with antituberculous chemotherapy. It is postulated

that adrenocortical steroids may have inhibited the inflammatory reaction and interfered with the natural tendency to fibrosis and thus have enhanced the possibility of a pneumothorax in this situation.

Sumario

Neumotórax Espontáneo durante la Esteroidoterapia de la Tuberculosis Pulmonar Muy Avanzada y Rápidamente Evolutiva

Hubo 2 casos de neumotórax espontáneo entre 7 enfermos de tuberculosis pulmonar muy avanzada y rápidamente evolutiva, que recibían esteroides córticosuprarrenales junto con quimioterapia antituberculosa. Presupónese que los esteroides tal vez inhibieran la reacción inflamatoria y obstaculizaran la tendencia natural a la fibrosis, acrecentando así la posibilidad de un neumotórax en dicha situación.

Resume

Pneumothorax spontané pendant la thérapeutique par les stéroides dans une tuberculose pulmonaire trés avancée et rapidement évolutive

Deux cas de pneumothorax spontané se produisirent parmi 7 malades présentant une tuberculose pulmonaire trés avançée, rapidement évolutive, qui reçurent des stéroides adrénocorticaux en même temps qu'une chimiothérapie antituberculeuse. On a assumé que les stéroides adrénocorticaux peuvent avoir inhibé la réaction inflammatoire et gêné la tendance naturelle à la fibrose, et avoir ainsi accru la possibilité d'un pneumothorax dans cette situation.

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INTRATHORACIC HIBERNOMA[1]

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Introduction

Hibernoma is a term used to describe a rare type of lipoma. The fat of which it is composed has been called "brown fat" in contrast to "yellow fat," and is found in different animals, including man. Lipomatous tumors of all types are rather uncommon in the chest. A personal observation of the rarest of these, the hibernoma, led the writers to search the literature for the experience of others. To the best of their knowledge, the following is the fifth thoracic hibernoma reported.

Case Report

L. W. (27646), a 26-year-old, white, unemployed, married male was admitted to the Veterans Administration Hospital, West Haven, Connecticut, on January 26, 1959, having been referred for evaluation of an abnormal chest roentgenogram. A sharply demarcated lesion in the periphery of the left hemithorax had slowly enlarged since it had been first noted four years before. Two weeks prior to admission, the patient had had an upper respiratory infection and right shoulder pain which lasted about four days; a nonproductive cough persisted. He denied fever, chills, night sweats, chest pain, or hemoptysis.

The patient had worked as a packer in a warehouse and had been a mason's apprentice prior to that. He served in the army from 1953 to 1955, and had been stationed in Massachusetts, Indiana, and Colorado. The past history revealed no serious illnesses. He had not smoked. Family history was noncontributory. A review of systems revealed an external otitis one year ago and a mild type of Raynaud's phenomenon of both hands and feet since 1954. The vasospastic symptoms had not progressed, and he was actually less aware of them than he had been in 1954.

On physical examination the patient was a well-nourished and well-developed man with a blood pressure of 130 systolic, 80 diastolic in mm. of mercury. His pulse was 90 per minute and temperature, 98.6°F. The only abnormal finding was coolness of the feet. All pulses were present. Color changes were not present and could not be produced by cold water immersion.

Laboratory studies showed a normal hemoglobin, hematocrit, and urinalysis. The serologic test for syphilis (VDRL), lupus erythematosus preparations, cryoglobulins, PPD reaction, and histoplasmin and coccidioidin reactions were negative. Cold agglutinins were absent. Sputum and gastric cultures were negative for acid-fast organisms. Serum proteins, including the electrophoretic pattern, and liver and renal function tests were normal. Other studies included pulmonary function and bronchoscopy, which were normal.

Roentgenograms of the chest (figures 1 and 2) demonstrated a smooth well-circumscribed homogeneous shadow measuring 4.5 cm. in diameter at the level of the left fourth rib posteriorly. Planigrams gave the impression that the lesion was attached to the chest wall and was not in the lung. A diagnostic pneumothorax (figure 3) confirmed this impression. No calcium was present in the shadow on any of the films. The principal diagnoses considered at this time were mesothelioma and neurofibroma.

Thoracotomy was performed on February 18, 1959, under endotracheal anesthesia with the patient in the right posterior oblique position. The fourth rib was removed subperiostally and the pleural space entered anterior to the tumor. A subpleural spherical mass was seen between the third and fifth ribs. The tumor was excised *en bloc* with portions of the third and fifth ribs and a free pleural margin. The chest wall defect was closed by using a small piece of dacron cloth. The closure was completed in the usual fashion. The postoperative course was uneventful, and the patient was discharged two weeks later. The vasospastic symptoms had not changed and were about the same one year later.

Pathology

Macroscopic examination: The tumor measured 4 cm. in diameter. It was perfectly spherical and encapsulated. Its consistency was rubbery and soft. On cut section, it was yellow-tan and solid except for one small cystic area (figure 4).

Microscopic examination: Microscopically, the tumor was identical with the hibernomas described in the literature. It was lobulated, vascular, and had a well-defined capsule attached to the pleura. The structure was loose, and the individual cells varied in size from 20 to 70 μ. The cells were round, polygonal, or ovoid. The cytoplasm of the smaller cells was eosinophilic and granular. Those intermediate in size contained in their cytoplasm numerous small and coalescing vacuoles. The larger cells contained locules, and

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FIG. 1 (Left). Postero-anterior roentgenogram. Note the smooth homogeneous density at the level of the fourth rib posterolaterally.
FIG. 2 (Center). Left lateral roentgenogram showing the well-circumscribed lesion in the left posterior hemithorax.
FIG. 3 (Right). Postero-anterior roentgenogram after diagnostic pneumothorax. The left lung is shown to drop away from the lesion on the chest wall.

FIG. 4. Gross specimen sectioned. Note the capsule beneath the pleura and the uniformity of the tumor except for the small cystic area.

the largest were unilocular. The nuclei were small with a tendency to be centrally placed and to have a prominent central nucleolus. Occasional nuclei were indented by adjacent vacuoles. Small accumulations of brown pigment, apparently a lipochrome, were present, and foci of plasma cells occurred in the septa and around some of the blood vessels (figures 5 and 6).

This case represents the thirty-ninth reported hibernoma and the fifth one found in the thorax.

The locations of the four intrathoracic hibernomas as seen roentgenographically in the cases previously reported are illustrated in figure 7. The ages of these patients were twenty-two, thirty-one, thirty-nine, and forty-two years. There were three males, one of whom was a Negro, and one female. Symptoms were present in three and one was asymptomatic. Pleural pain was present in two, cough in two, wheezing in one, and numbness in the arm in one. The wheezing in one patient was due to bronchial compression by a very large tumor (1). Numbness in the arm, reported with the hibernoma shown as No. 3 in figure 7, was unexplained (3). In the present case, the presenting symptoms were due to an incidental upper respiratory infection. All four hibernomas reported were located on the posterolateral chest wall. Three were on the left side, and one on the right. The roentgenographic appearance of each was that of a smooth, well-defined, round, or lobulated lesion arising from the posterolateral chest wall. Three of the four patients who had been followed roentgenographically showed slow progressive enlargement. No calcification has been reported. Hibernomas cast a denser shadow than ordinary lipomas, presumably because of their vascularity and high percentage of phospholipid and glycogen (1). The large tumor reported by Kittle and associates (1) showed small areas of degeneration but no hemorrhage. The color of these tumors on cut surface has varied from tan to yellow-brown to grayish-orange. The color is probably due to a lipochrome pigment plus the rich vascularity of the hibernoma. All were spongy, glistening, and elastic.

DISCUSSION

The hibernoma type of tumor was probably first described in man by Merkel (5) in 1905. In

1914, Gery (6) suggested the name "hibernoma" because of its similarity to hibernating glands of certain mammals. The term has persisted although other names such as lipoma granulare (granular cell lipoma), atypical lipoma, pseudolipoma, lipoblastic lipoma, brown adenomorphous lipoblastoma, and embryonic brown lipoma, have been applied. In 1951, Gery himself denounced the term "hibernoma" and referred to it as a "sin of his youth." It is an incorrect term because brown fat does not control hibernation; moreover, it is not clear whether the brown fat found in man is the same as that in the hibernating glands of animals, in spite of the microscopic similarity.

Brown fat was described as long ago as 1670 by Velsch, and since has been found in more than

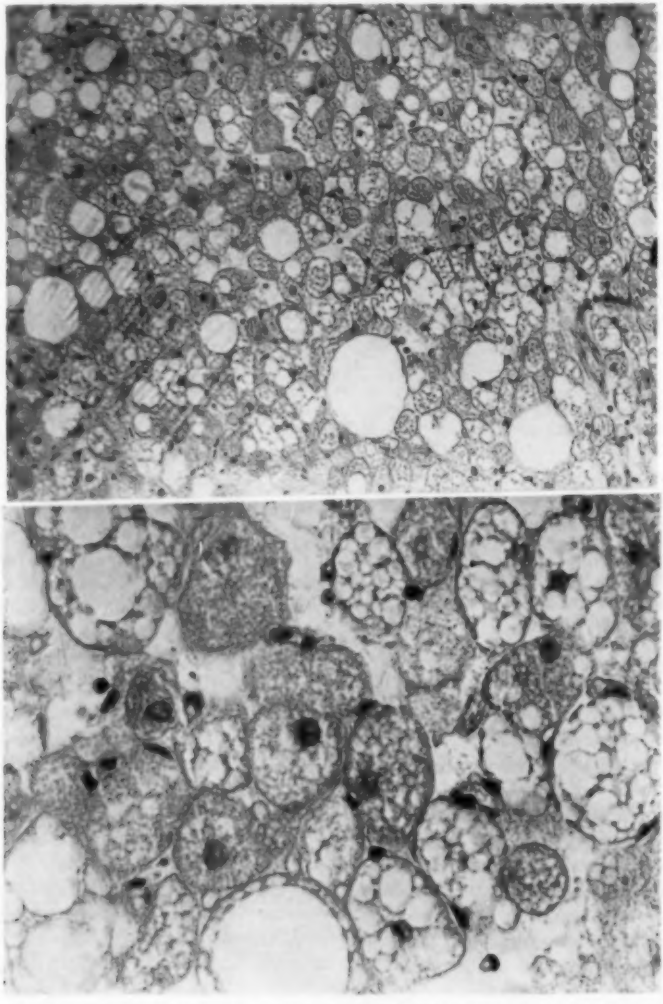

FIG. 5 (Upper). Low-power photomicrograph of tumor, showing lack of uniformity of vacuolization of cells, with gradation from nonvacuolated granular cells to unilocular cells.

FIG. 6 (Lower). High-power photomicrograph from center of figure 5, showing small sharply delineated nuclei with prominent nucleoli. Occasional nucleus is distorted by vacuoles (upper right corner).

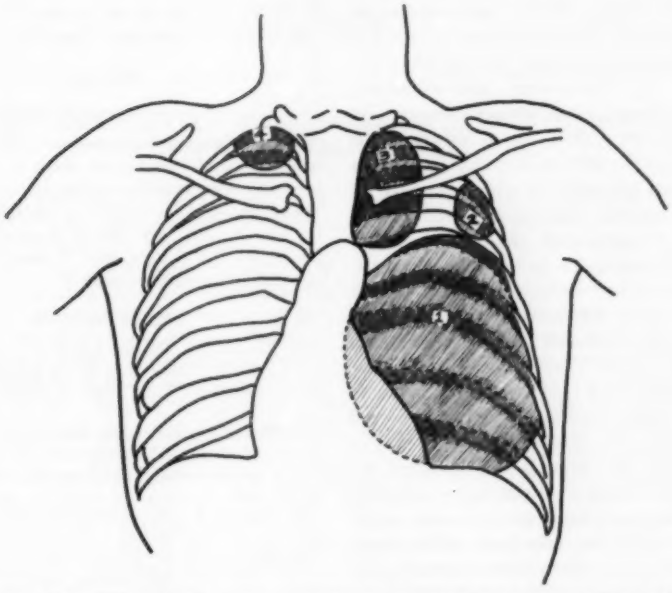

FIG. 7. Locations of intrathoracic hibernomas previously reported (*see* corresponding references 1–4).

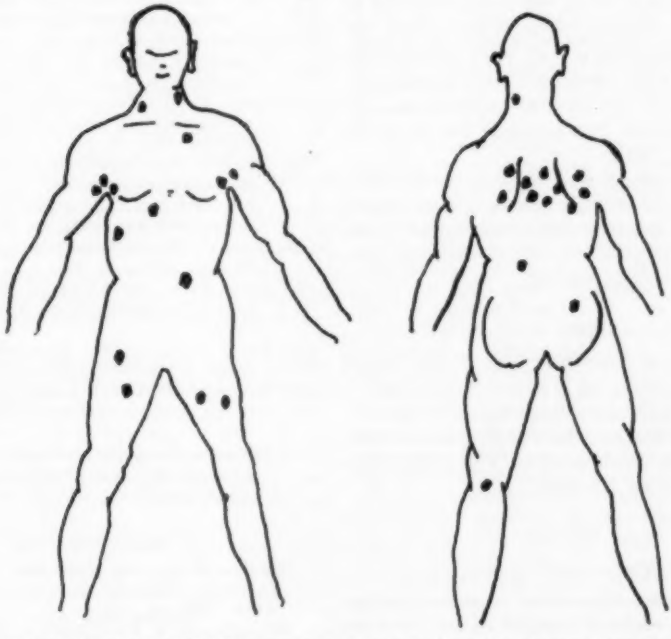

FIG. 8. Approximate locations of 29 hibernomas reported outside of the thorax. Note the similarity to the distribution of hibernating fat in animals, as described by Rasmussen (11).

fifty different animals. While most common in hibernating animals, it is also found in the rat, mouse, monkey, and in man. In 1902, Shaw (7) pointed out that the axillary and subpleural areas in the human fetus contained brown fat in contrast to the yellow fat of subcutaneous tissues. Hatai (8) in 1908 showed that the human embryo had an interscapular glandlike mass resembling the animal hibernating gland. Later, Bonnot (9) demonstrated the persistence of brown fat into adult life in those locations described in the human embryo and fetus. In the adult, brown fat is regularly found as scattered islands along the esophagus, trachea, large vessels of the mediastinum, dorsocervical, and interscapular regions, and also around the kidneys (10). Hibernomas reviewed by Beetstra and Quast (4) have a distribution similar to that of hibernating fat in animals as described by Rasmussen (11) (figure 8). His anatomic dissection in animals demonstrated a primary mass in the mediastinum extending into both axillas, neck, back, perineal and retroperitoneal tissues, and even into the inguinal and gluteal regions.

Melicow (12) pointed out the presence of brown fat (hibernoma type) in the pericapsular fat of sixteen of eighteen pheochromocytomas resected. A relationship may exist between the stress phenomenon associated with pheochromocytoma and the development of brown fat. The possible diagnostic significance of this should be investigated further.

Malignant change has not been reported in a hibernoma. "Precordial bodies" have shown malignancy, but these differ histologically from brown fat. The possibility of a relationship, however, has been suggested (13).

Summary

The thoracic hibernoma is a benign tumor arising from brown fat in the subpleural regions. Four cases of thoracic hibernomas previously reported in the literature have been reviewed briefly and a fifth case has been added. This is the thirty-ninth hibernoma reported.

Sumario

Hibernoma Intratorácico

El hibernoma torácico es un tumor benigno que tiene su origen en el tejido adiposo pardo de las regiones subpleurales. Se repasan sucintamente 4 casos de hibernomas torácicos ya descritos en la literatura y se agrega un caso nuevo. Este el trigésimonono hibernoma descrito.

Resume

Hibernome intrathoracique

L'hibernome intrathoracique est une tumeur bénigne ayant son origine dans le tissu adipeux brun des régions subpleurales. Quatre cas d'hibernomes thoraciques rapportés auparavant dans la littérature ont été revus rapidement et un cinquième cas a été ajouté. Celui-ci est le trente neuvième hibernome rapporté.

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Notes

AN INCREASED EFFECT WITH INCREASED DOSAGE OF ISONIAZID IN EXPERIMENTAL TUBERCULOSIS

Except for limited clinical trials on "high isoniazid dosage," it has been common practice in most countries to treat all forms of tuberculosis with isoniazid dosages well below the limit that the toxicity of this drug would allow. This practice relies more or less implicitly on the belief that experiments on animals have shown a "maximal effective concentration" over which any further increment in drug dosage will result in no further improvement of the results.

Indeed, this is the case in many published experiments. For obvious practical reasons, in the experimental model used for the screening of antituberculous drugs, mice are infected with tubercle bacilli, treatments are started at the same time, and results are estimated over a short observation period. The surviving mice are sacrificed either at the end of a three- or four-week treatment period or shortly thereafter, the effects of treatment being expressed as differences in tuberculous lesions, percentage of survivors, or prolongation of median survival time, within a short period. Judging by such criteria, a dosage of 2.5 or 5 mg. of isoniazid per kg. per day is one of such efficiency that no further improvement can be gained from a further increase in the dosage. This dosage happens to give concentrations of isoniazid in the blood of humans well above those needed to prevent growth of tubercle bacilli *in vitro*.

McCune and associates[1] have shown that once a certain level of isoniazid dosage had been attained, the phenomenon of microbial persistence of tubercle bacilli in the spleens of infected mice remained uninfluenced by a fivefold further increase in isoniazid dosage.

In discussing this observation, these investigators make a more general statement concerning the effects of an increased dosage on any effect (not only microbial persistence) of any drug on any microbial species. They state ". . . there is a range within which increases in drug dosage produce increased effects, but a limit is soon reached and above that limit further increments of drug dosage serve no useful purpose. The upper limit of this range represents the familiar abstract concept of a maximal drug concentration for a particular drug parasite interreaction."

The particular drug parasite interreaction involved in the experiments of McCune and associates was that occurring when mice were infected with tubercle bacilli and started on isoniazid treatment at the same time. It has been demonstrated[2] that isoniazid is less effective in terms of reducing populations of tubercle bacilli when the infection has been allowed to progress to the point of microscopic tubercles than when drug and infection are started together. As from these observations and others it is clear that the nature of the lesion exerts an important influence on the response of tubercle bacilli to an antimicrobial drug, it seemed worth while to compare the upper limit over which increases in drug dosage apparently do not produce increased effect in two different situations: one in which isoniazid treatment was started at the same time as infection, and one in which the effect of greater dosages on advanced lesions in an experimental infection in mice was studied. Moreover, as any drug administered by the oral route may be irregularly absorbed by very sick animals, it was decided to conduct the experiments with the administration of isoniazid, but by the subcutaneous route.

Albino mice ("Rockefeller Institute" bred in France) were infected by the intravenous route with a bovine strain of *M. tuberculosis*. The inoculum consisted of colonies grown on Löwenstein-Jensen egg medium emulsified in 0.5 per cent bovine albumin. By plating dilutions on Dubos agar medium, it was determined that the 0.2-ml. inoculum used contained about 10^6 culturable units of tubercle bacilli.

The isoniazid was administered by the subcutaneous route once daily except on Saturdays and Sundays for a total of 21 injections.

In one group, drug administration was started one day after infection. In the other experimental group, drug administration was postponed until the twentieth day after infection, at which time the untreated animals were all acutely ill and 15 of 63 had already died of the tuberculous infection.

The daily isoniazid dosages employed were 2 mg., 10 mg., and 50 mg. per kg. of body weight.

The results are presented in table 1 and figure 1. As may be seen, judging from the seventy-day observation point, the 10-mg. per kg. dosage of

[1] McCune, R. M., *et al.*: Amer Rev Tubere, 1957, *76*, 1106.

[2] McCune, R. M., *et al.*: J Exp Med, 1956, *104*, 763.

TABLE 1

RESULTS OF TREATMENT WITH ISONIAZID
(2, 10, and 50 Mg. per Kg. per Day in Early and Late Administration)

Days of Treatment (after Infection)	Isoniazid Dosage (Mg./Kg./Day Subcutaneous'y)	Survival of Individual Mice (Number of Days after Infection)
	Untreated controls: died before late treatments were begun died after late treatments were begun	13, 16, 18, 19, 20, 20, 20, 20, 20, 20, 20, 20, 20, 20, 20, 20 22, 23, 24, 24, 27, 27, 27, 27, 34, 48, 49, 62, S
1st to 28th	Isoniazid 2 10 50	23, 48, 48, 48, 53, 56, 56, 57, 58, 69 73, 76, 77, 84, 91, 97, S, S, S 134, S, S, S, S, S, S, S, S, S
20th to 45th	Isoniazid 2 10 50	22, 22, 24, 27, 27, 27, 28, 30, 45, 46, 49, 69 21, 21, 21, 27, 27, 27, 59, 59, 62, 62, 75, S 21, 21, 21, 23, 64, 84, 84, 104, S, S, S

S = Killed 171 days after infection.

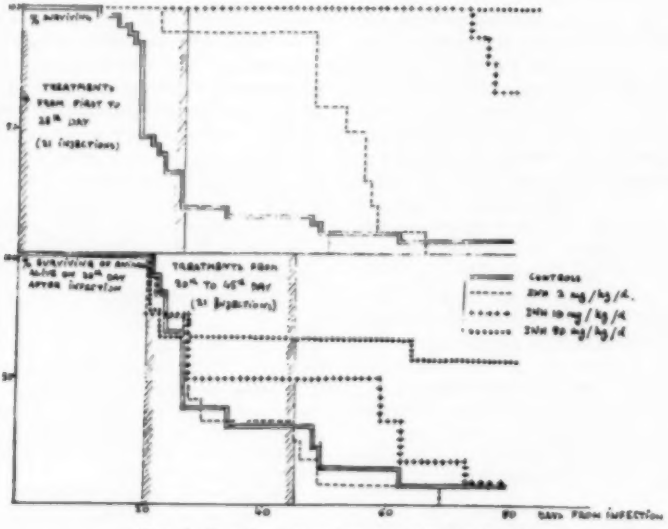

FIG. 1. Results of treatment with isoniazid.

isoniazid can be considered as the upper-limit of the effective dosage of this drug when drug administration and infection are started together. At the 2-mg. per kg. daily dosage, isoniazid given subcutaneously for three weeks produced a very significant prolongation in the survival time. A fivefold increase in drug dosage, i.e., to 10 mg. per kg., in this experimental model resulted in an improved effect. No mortality occurred either at 10 mg. per kg. per day or at 50 mg. per kg. per day, so that no superiority of the 50-mg. per kg. dosage was detectable judging from the already rather long observation period.

When the beginning of drug administration was delayed until the twentieth day of infection, hardly any effect was obtained with 2 mg. of isoniazid per kg. per day. With the next increment of dosage (fivefold), the survival time was lengthened and the results were still further improved by the top level of dosage, 50 mg. per kg. per day. Thus, it may be seen that a dose of isoniazid that is quite effective in previously undamaged tissue

TABLE 2

RESULTS OF TREATMENT WITH ISONIAZID (50 and 100 Mg. per Kg. per Day in Late Administration)

Isoniazid Dosage (Mg./Kg./Day Subcutaneously)	Survival of Individual Mice (Number of Days after Infection)
Untreated controls	13, 14, 15, 15, 16, 16, 16, 16, 17, 17, 17, 20, 22, 27
Isoniazid 50	14, 14, 14, 15, 15, 15, 16, 17, 17, 20, 22, 22, 22, 24, 25
100	15, 15, 15, 16, 16, 16, 20, 22, 23, 24, 24, 25, 25, 25, 27, 27

may become completely ineffective in the presence of more advanced infection.

Moreover, even when treatment was begun at the time of infection, it was only necessary to prolong the observation period beyond its usual limits to see that the effects on survival of the 50-mg. per kg. per day dosage were definitely superior to those obtained at the 10-mg. dosage level.

In short, a definite dosage-response effect was observed in all circumstances. Moreover, no upper limit was found to the effective concentration, within the range of dosage employed in the present experiment, so long as the period of observation was not arbitrarily limited.

In the experiments by McCune and associates, using a different drug-microbe situation, it was shown that 24 mg. of isoniazid per kg. daily were superior to 6 mg. per kg., but that 100 mg. per kg. produced no greater effects than the dosage level of 24 mg. per kg. In the present experiments, using a different drug-microbe situation and a different criterion of effect, it was found that 10 mg. per kg. were definitely superior to 2 mg. per kg. and that 50 mg. per kg. were superior to 10 mg. per kg. From both sets of experiments, therefore, it is clear that an isoniazid dosage of somewhere between 10 and 50 mg. per kg. per day is definitely superior to 10 mg. itself and lesser daily dosages of the drug. Whether, in the present experimental model, a ceiling would be reached between 50 and 100 mg. per kg. cannot be stated because the 50-mg. dosage level was the highest one employed. To try to answer this question, another experiment was performed, using the same experimental model and comparing 50 to 100 mg. of isoniazid per kg. per day given in delayed treatments of three weeks by subcutaneous administration. The dosage of 100 mg. per kg. was chosen because it was the highest dosage used in the experiments by McCune and because, when isoniazid is given subcutaneously, it is about the highest tolerated dose.

The mice, the strain of tubercle bacilli, the preparation of the inoculum, and the treatments were as in the first experiment, except that the inoculum was larger (about 2.5×10^6 viable units) and that, the infection being more acute, the administration of isoniazid was started on the thirteenth day after infection. The daily isoniazid dosage employed was 50 and 100 mg. per kg. per day.

The results are presented in table 2. As may be seen, isoniazid at the 50-mg. per kg. per day dosage had hardly any effect on this more acute infection. Increasing the dosage to 100 mg. per kg. per day resulted in a definitely superior effect. In view of these facts, the writers are in agreement with the statement of McCune and associates that "in current clinical use . . . the maximal daily dosage of the antimicrobials . . . should be largely determined by considerations of drug toxicity." In other words, as stated by McDermott,[3] "effective concentration . . . represents an abstraction," and the dosage of any drug should be as large as can be administered without entailing serious risk of drug toxicity.

In summary: A definite dosage-response effect has been demonstrated by isoniazid on experimentally induced tuberculous infection in mice. Moreover, the effect of lower levels of isoniazid dosage was largely abolished when administration of the drug was withheld until extensive lesions had developed. Even in these circumstances, however, the dosage-response effect was evident and higher dosages of isoniazid were clearly superior.

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[3] MCDERMOTT, W.: In *Bacterial and Mycotic Infections in Man*, ed. 3, J. B. Lippincott Co., Philadelphia, 1958, p. 694.

[4] With the technical assistance of Monique Lacueil.

URINE CULTURES IN TUBERCULOSIS[1]

Asymptomatic renal tuberculosis is probably more common than has formerly been assumed. Numerous publications by clinicians to this effect have been confirmed by 5,424 necropsy studies by Medlar, Spain, and Holliday.[2] The bacteriologic diagnosis of tuberculosis of the genitourinary tract is, therefore, all the more important, and the most suitable methods should be adopted for routine study of urine cultures for *Mycobacterium tuberculosis*.

It has been generally accepted that 24-hour urine specimens should be used for the isolation of *M. tuberculosis*. This is based on the supposition that tubercle bacilli may be present in such small numbers as to render isolation from small samples of urine very difficult. However, few hospitals are equipped for refrigeration of bulky 24-hour specimens during collection, and overwhelming contamination often occurs. The collection of 24-hour specimens is often impracticable in ambulatory patients. Furthermore, 24-hour specimens necessitate an additional day for sedimentation. Often, not all of the sediment can be processed and, thus, only part of the bacillary population is cultured, thereby defeating the purpose of the 24-hour collection. Because of these problems, it appeared worth while to conduct a comparative study of 24-hour and morning urine specimens from tuberculous patients in order to evaluate their true usefulness in the isolation of *M. tuberculosis*.

In a preliminary study, urine specimens artificially seeded with *Mycobacterium tuberculosis* were used. To urine collected as usual, known dilutions of suspensions of *M. tuberculosis* were added, so that paired samples of urine, one 24-hour and one morning specimen, contained theoretically the same number of organisms per milliliter. In one group, urine samples contaminated with other bacteria were used. In the other group, the urine specimens were autoclaved before seeding with tubercle bacilli. All urine samples were treated with 4 per cent sodium hydroxide. The 24-hour specimens were sedimented overnight; the morning specimens were centrifuged. All were cultured on three tubes of American Trudeau Society medium.[3] A total of 688 cultures were thus performed on urine samples artificially seeded with *M. tuberculosis*.

TABLE 1

PERCENTAGE OF CULTURES POSITIVE FOR M. TUBERCULOSIS OF STERILE 24-HOUR AND MORNING URINE SPECIMENS SEEDED WITH KNOWN CONCENTRATIONS OF M. TUBERCULOSIS

	24-Hour Urine Treated with Sodium Hydroxide	Morning Urine Treated with Sodium Hydroxide	Untreated Morning Urine
Total number of cultures	84.0	84.0	84.0
Number of positive cultures	15.0	72.0	69.0
Per cent of positive cultures	17.8	85.7	82.1

The second study was performed on urine collected at random from hospitalized patients. A total of 3,612 cultures were done, half on 24-hour specimens, and half on morning urine. Half were treated with trisodium phosphate, and half with sodium hydroxide. Many of the specimens were from patients with urinary tract infections and were heavily contaminated with various microorganisms. When urine was collected from tuberculous patients under antimicrobial treatment, the treatment was suspended, as recommended by Kenney, Lattimer, and Goldman,[4] for at least one week prior to the collection.

In table 1 it may be seen that, in 84 sterile urine samples artificially seeded with *M. tuberculosis*, only 15 cultures (17.8 per cent) were positive for *M. tuberculosis* from 24-hour specimens, while 72 (85.7 per cent) were found positive for *M. tuberculosis* in morning urine treated with sodium hydroxide, and 69 (82.1 per cent) in untreated morning urine. In table 2 it may be seen that, when sterile urine was seeded with serial dilutions of *M. tuberculosis*, even the heavily seeded specimens yielded far fewer positive cultures for *M. tuberculosis* in the 24-hour group than in the morning specimens. This difference in recovery became even more marked when the number of tubercle

[1] The preliminary report on this study was presented at the 59th general meeting of the Society of American Bacteriologists, St. Louis, Missouri, May 10–14, 1959.

[2] MEDLAR, E. M., *et al.*: J Urol, 1949, *61*, 1078.

[3] STEENKEN, W., JR.: Medium recommended on evaluation of laboratory procedures of the American Trudeau Society for the culture of tubercle bacilli, Trudeau Laboratory, Saranac Lake, New York.

[4] KENNEY, M., *et al.*: Amer Rev Tuberc, 1954, *70*, 149.

TABLE 2

PERCENTAGE OF CULTURES POSITIVE FOR M. TUBERCULOSIS OF STERILE 24-HOUR AND MORNING URINE SPECIMENS SEEDED WITH SERIAL DILUTIONS OF M. TUBERCULOSIS

Dilutions	24-Hour Urine Treated with Sodium Hydroxide			Morning Urine Treated with Sodium Hydroxide			Untreated Morning Urine		
	Number of Cultures	Number Positive	Per Cent Positive	Number of Cultures	Number Positive	Per Cent Positive	Number of Cultures	Number Positive	Per Cent Positive
1:1	12	9	75	12	12	100	12	12	100
1:10	12	3	25	12	12	100	12	12	100
$1:10^2$	12	0	0	12	12	100	12	9	75
$1:10^3$	12	3	25	12	12	100	12	12	100
$1:10^4$	12	0	0	12	9	75	12	9	75
$1:10^5$	12	0	0	12	9	75	12	9	75
$1:10^6$	12	0	0	12	6	50	12	6	50

bacilli was decreased by serial dilutions. The percentage of recovery of *M. tuberculosis* from both 24-hour urine and morning urine artificially seeded with *M. tuberculosis* was far less in unsterile urine specimens. However, the same proportion of recovery was observed, morning specimens giving far better results than 24-hour specimens, as is demonstrated in tables 3 and 4. In tables 5, 6, and 7 results may be seen of comparative studies on 24-hour and morning urine specimens collected at random from hospitalized patients.

In table 5 it may be seen that, when treated with sodium hydroxide, the morning urine samples yielded 27 cultures positive for *M. tuberculosis* from a total of 903 cultures (2.9 per cent), as compared with 18 positive cultures (2.0 per cent) isolated from 24-hour specimens. The percentage of recovery of *M. tuberculosis* from both 24-hour and morning urine specimens was the same when the specimens were treated with trisodium phosphate.

The percentage of recovery of chromogenic acid-fast organisms was also much higher from morning urine when sodium hydroxide was used (table 6). Thus, 39 of 903 cultures (4.3 per cent) were obtained from morning specimens, as compared with 15 of 903 (1.6 per cent) obtained from 24-hour specimens.

The rate of contamination was, as expected, far greater in 24-hour urine than in morning urine specimens, as may be seen in table 7. This was true in urine treated either with sodium hydroxide or trisodium phosphate.

Another finding evident from detailed analysis of all cultures, but not presented in any of the tables, was that cultures positive for *M. tuberculosis* were not always found in the same patient in both 24-hour and morning urine specimens. In fact, in some cases, positive cultures were obtained from morning specimens exclusively. However, in fewer cases, only 24-hour urine yielded *M. tuberculosis*.

TABLE 3

PERCENTAGE OF CULTURES POSITIVE FOR M. TUBERCULOSIS OF CONTAMINATED 24-HOUR AND MORNING URINE SPECIMENS SEEDED WITH KNOWN CONCENTRATIONS OF M. TUBERCULOSIS AND TREATED WITH SODIUM HYDROXIDE

	24-Hour Urine	Morning Urine
Total number of cultures	88.0	88.0
Number of positive cultures	9.0	40.0
Per cent of positive cultures	10.2	45.4

TABLE 4

PERCENTAGE OF CULTURES POSITIVE FOR M. TUBERCULOSIS OF CONTAMINATED 24-HOUR AND MORNING URINE SPECIMENS SEEDED WITH SERIAL DILUTIONS OF M. TUBERCULOSIS AND TREATED WITH SODIUM HYDROXIDE

Dilutions	24-Hour Urine			Morning Urine		
	Number of Cultures	Number Positive	Per Cent Positive	Number of Cultures	Number Positive	Per Cent Positive
1:1	22	6	27.3	22	11	50.0
1:10	12	1	8.3	12	8	66.7
$1:10^2$	12	1	8.3	12	9	75.0
$1:10^3$	12	0	0	12	8	66.7
$1:10^4$	12	1	8.3	12	3	25.0
$1:10^5$	9	0	0	9	1	8.3
$1:10^6$	9	0	0	9	0	0

TABLE 5

PERCENTAGE OF CULTURES POSITIVE FOR M. TUBERCULOSIS OF 24-HOUR AND MORNING URINE SPECIMENS

	24-Hour Urine		Morning Urine	
	Treated with Trisodium Phosphate	Treated with Sodium Hydroxide	Treated with Trisodium Phosphate	Treated with Sodium Hydroxide
Total number of cultures	903	903	903	903
Number of positive cultures	3	18	3	27
Per cent of positive cultures	0.3	2.0	0.3	2.9

TABLE 6

PERCENTAGE OF CULTURES POSITIVE FOR CHROMOGENIC ACID-FAST BACILLI OF 24-HOUR AND MORNING URINE SPECIMENS

	24-Hour Urine		Morning Urine	
	Treated with Trisodium Phosphate	Treated with Sodium Hydroxide	Treated with Trisodium Phosphate	Treated with Sodium Hydroxide
Total number of cultures	903	903	903	903
Number of positive cultures	6	15	0	39
Per cent of positive cultures	0.7	1.6	0	4.3

TABLE 7

PERCENTAGE OF CONTAMINATION IN CULTURES FOR M. TUBERCULOSIS OF 24-HOUR AND MORNING URINE SPECIMENS

	24-Hour Urine		Morning Urine	
	Treated with Trisodium Phosphate	Treated with Sodium Hydroxide	Treated with Trisodium Phosphate	Treated with Sodium Hydroxide
Total number of cultures	903	903	903	903
Number of contaminated cultures	96	171	6	57
Per cent of contaminated cultures	10.6	18.9	0.7	6.3

Comparative studies of urine artificially seeded with known numbers of *M. tuberculosis*, conducted on both contaminated and sterile urine, permit some conclusions on the cause of the far better recovery of *M. tuberculosis* from morning specimens. While these results in unsterile urine could be ascribed to a lower rate of contamination of the cultures from morning specimens, the lesser recovery of *M. tuberculosis* from sterile 24-hour urine must be due to a dilution phenomenon. Since the rate of recovery of *M. tuberculosis* was the greatest in sterile morning specimens, it appears that both factors—the dilution and the contamination—reduced the recovery from 24-hour urine. Apparently, the same factors operated in the routinely collected urine samples, with less spectacular but, nevertheless, appreciably higher recovery from morning urine specimens.

The incidental findings in the studies of urine artificially seeded with *M. tuberculosis* were that treatment with 4 per cent sodium hydroxide, not exceeding a total time of forty-five minutes, did not have any appreciable bactericidal effect on *M. tuberculosis*, and that treatment with sodium hydroxide allowed better recovery of *M. tuberculosis* than did treatment with trisodium phosphate.

The fact that cultures positive for *M. tuberculosis* were not always found in all of the specimens from the same patients points once more to the intermittent nature of the discharge of *M. tuberculosis* into the urinary tract. This emphasizes the need of more frequent culture of urine when tuberculosis of the genitourinary tract is suspected. The technical ease with which morning urine can be processed, as compared with the 24-hour specimens, and the better recovery rate obtained in morning urine appear to indicate that there is no advantage in using 24-hour specimens for isolation of *M. tuberculosis* from urine, and that morning specimens should be used.

In summary: A comparative study of cultures for *M. tuberculosis* was made on 24-hour and morning urine specimens. The total of 4,300 cultures included 688 cultures made from urine artificially seeded with known dilutions of *M. tuberculosis* and 3,612 cultures from urine routinely collected from hospitalized patients. All of the studies demonstrated a greater rate of contamination of cultures obtained from 24-hour collections of urine, and a greater recovery of both *M. tuberculosis* and chromogenic acid-fast bacilli from morning urine specimens. It is necessary to culture the urine frequently in cases of suspected

tuberculosis of the genitourinary tract. Consequently, in view of the relative ease with which morning urine specimens can be processed and the greater percentage of recovery of *M. tuberculosis* from morning urine samples, it appears that there is no advantage in 24-hour collections of urine, but that morning urine specimens should be used.

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CHARACTERISTICS OF MYCOBACTERIAL POPULATIONS FOUND IN THE SPUTUM OF TUBERCULOUS PATIENTS AFTER PROLONGED ISONIAZID THERAPY

Although isoniazid has now been in use since 1952, there is scant information on the true characteristics of the microbial populations found in the sputum of patients who still have infectious pulmonary tuberculosis despite prolonged treatment with this drug. Improved knowledge of the composition of the various mixtures of tubercle bacilli in the sputum of such patients could lead to a better understanding of the many problems related to: the clinical significance of drug-susceptibility tests, the potential infectiousness of patients who are "treatment failures," the need to continue isoniazid in such cases for indefinite periods of time, and problems related to the transmission of isoniazid-resistant organisms to uninfected persons.

It was the purpose of the present study to accumulate some precise information about the types and distribution of tubercle bacilli as they were found in the sputum of tuberculous patients still infectious after extensive treatment with isoniazid administered either alone or with various combinations of other agents.

The series of patients whose sputum specimens were used in this study consisted mostly of males of the average age of fifty-five years, with long-standing active pulmonary tuberculosis. Their sputum had remained infectious in spite of their having been on continuous isoniazid therapy for at least two years, as far as could be determined from a careful review of their clinic charts. Only a single sputum specimen from each of 50 patients was taken for this study, and 46 of the resulting populations of tubercle bacilli were considered suitable. Four were too heavily contaminated.

The sputum specimens were digested by the trisodium phosphate transport-digest method.[1] Two stained smears were prepared from each concentrate, and Gaffky counts of acid-fast bacilli were made on 20 fields of each smear to determine the dilution necessary to ensure discrete colony growths for counting. Direct drug-susceptibility tests[2] were performed on Peizer-Schechter duplicate agar plates.[3] The control cultures (no isoniazid) representing the entire unaltered mixtures of bacillary populations of tubercle bacilli, as found in the sputum, were tested for catalase activity, isoniazid susceptibility, and guinea pig virulence, using methods as previously described.[4, 5] Isoniazid-susceptibility and catalase-activity tests were also carried out on the populations of tubercle bacilli isolated from guinea pig tissues.

On the basis of the guinea pig virulence of the populations of tubercle bacilli isolated from the 46 specimens of sputum and the isoniazid susceptibility and catalase activity of the tubercle bacilli resulting from culture of the infected guinea pig tissues, there appeared to be five general types of populations of tubercle bacilli found in the sputum. These may be described as follows:

(*1*) Variously isoniazid-resistant, highly catalase-active (75 to 100 per cent) populations of tubercle bacilli, virulent for guinea pigs, in which there occurred a shift to increased isoniazid susceptibility on guinea pig passage. For example, population No. 4 in table 1 appeared to be susceptible to 10 γ and completely resistant to 25 γ of isoniazid per ml. of medium. However, the culture of tubercle bacilli isolated from infected guinea pig tissue was susceptible to 1 γ per ml. and only partially resistant to 5 γ per ml. There were 13 of the 46 populations of tubercle bacilli virulent for guinea pigs in which the susceptibility to isoniazid increased on guinea pig passage.

(*2*) Variously isoniazid-resistant moderately catalase-active (50 to 75 per cent active) populations of tubercle bacilli found in sputum which were virulent for guinea pigs and which remained unchanged in isoniazid susceptibility on guinea pig passage. There were 13 such populations.

(*3*) Variously isoniazid-resistant, poorly catalase-active (25 to 50 per cent active) populations of tubercle bacilli isolated from sputum which did not produce apparent disease in guinea pigs. The animals sacrificed one year after infection showed no gross tuberculous lesions of lungs, liver, or spleen. However, the sparse cultures of tubercle bacilli (1 to 6 colonies) isolated from the guinea pig tissues had a tendency to increased isoniazid susceptibility. Primary culture No. 12, table 1, consisted of a population of tubercle bacilli entirely resistant to 5 γ per ml.; in addition, 75 per cent of the population was also resistant to 10 γ per ml.,

[1] PEIZER, L. R., *et al.*: Amer Rev Tuberc, 1954, *70*, 363.

[2] PEIZER, L. R., *et al.*: Amer J Clin Path, 1951, *21*, 982.

[3] PEIZER, L. R., AND SCHECHTER, C.: Amer J Clin Path, 1950, *20*, 642.

[4] PEIZER, L. R., AND WIDELOCK, D.: Amer Rev Tuberc, 1955, *71*, 305.

[5] PEIZER, L. R., AND WIDELOCK, D.: Amer Rev Tuberc, 1955, *72*, 246.

25 per cent to 25 γ per ml., and a few colonies to 100 γ per ml. The population of tubercle bacilli isolated from guinea pig tissues one year after infection with this culture consisted of about 25 per cent of organisms susceptible to 5 γ per ml. and 75 per cent susceptible to 1 γ per ml. The catalase activity of this population also changed from low (less than 25 per cent) to high (75 to 100 per cent). Five populations of this type appeared.

(*4*) Variously isoniazid-resistant, poorly catalase-active (10 to 25 per cent active) populations of tubercle bacilli isolated from sputum which, when passed through guinea pigs, produced no visible disease in the animals. However, sparse cultures of tubercle bacilli isolated from tissues of the sacrificed infected guinea pigs one year after infection remained essentially unchanged in isoniazid susceptibility and catalase activity. There were 8 such populations of tubercle bacilli.

(*5*) Variously isoniazid-resistant, poorly catalase-active (10 to 25 per cent active) populations of tubercle bacilli which were not virulent for guinea pigs, producing no apparent disease in the guinea pigs, and which yielded negative culture results from the animal tissues one year after infection. There were 7 such populations of tubercle bacilli isolated from 7 different specimens of sputum.

The primary culture results, isoniazid susceptibility, and catalase activity of the populations of tubercle bacilli isolated from single sputum specimens of the 46 patients are set forth in table 1. All of the 46 populations of tubercle bacilli were resistant to 0.1 γ of isoniazid per ml. of medium; 5 of the 46 populations of tubercle bacilli were susceptible to 1 γ per ml.; 12, to 5 γ per ml.; 17, to 10 γ per ml.; 20 were susceptible to 25 γ per ml.; 27, to 50 γ per ml.; and 31 of the populations of tubercle bacilli were susceptible to 100 γ per ml. Fourteen of the cultures were resistant to 100 γ per ml.

Variations in degree of isoniazid resistance and catalase activity of populations of tubercle bacilli isolated from the single sputum specimens of patients on drug therapy for two years or more were very diverse, as may be seen in table 1. However, the catalase activity of such isoniazid-resistant populations appeared to be a fair index of guinea pig virulence, irrespective of the degree of drug resistance. This was illustrated by the summarized results in figure 1. For example, as shown in figure 1, 20 guinea pigs died of tuberculous disease after infection with 20 different populations of tubercle bacilli of high and moderately high catalase activity (50 to 100 per cent), irrespective of the isoniazid resistance of the populations.

The intent to correlate the cultural characteristics of the populations of tubercle bacilli with the course of tuberculosis of the patients from whose specimens they were isolated proved to be impracticable, since it required about eighteen months to obtain all of the experimental results, during which time the patients were continued on isoniazid therapy. At the end of the study, 15 of the original 46 patients had died; 6, of causes other than tuberculosis, and 9, of tuberculosis usually complicated by intercurrent disease. Of the 31 patients still alive and still receiving isoniazid alone or in combination with other drugs, 6 had active infectious pulmonary tuberculosis with roentgenographic deterioration; 6 had cavitary pulmonary tuberculosis stabilized for at least one year, during which time all sputum cultures remained negative for tubercle bacilli; 19 had essentially stabilized active infectious pulmonary tuberculosis with slight improvement.

It was impossible to make any analogies of the behavior of the isolated isoniazid-resistant populations of tubercle bacilli in man, either in respect to pathogenicity or infectivity, with the effect of these populations on normal guinea pigs. Middlebrook and co-workers[6] have shown that the visceral, noncavitary lesions, induced experimentally in normal guinea pigs by infection with isoniazid-resistant catalase-negative tubercle bacilli, regress and heal. This occurred in 7 instances in this study. On the other hand, Oestereicher and associates[7] inferred from their observations that catalase-negative, isoniazid-resistant tubercle bacilli probably multiply in human "open" tuberculous cavities as fully as drug-susceptible, catalase-active organisms do.

Studies of infectivity of isoniazid-resistant tubercle bacilli for man are at present not conclusive. Chaves and associates[8] found 3 of 385 sputum specimens of previously untreated patients which contained tubercle bacilli resistant to 1 or 5 γ of isoniazid per ml. of medium. Other published reports[9-11] on the infectivity of isoniazid-resistant mutants of man are generally inconclusive at the present time.

In summary: A study was made of the characteristics of isoniazid-resistant populations of

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[6] Middlebrook, G., *et al.*: Amer Rev Tubere, 1954, *70*, 852.

[7] Oestereicher, R., *et al.*: Amer Rev Tubere, 1955, *71*, 390.

[8] Chaves, A. D., *et al.*: Amer Rev Tubere, 1955, *72*, 143.

[9] Melnotte, P., *et al.*: Rev Tubere (Par), 1955, *19*, 712.

[10] Debré, R., *et al.*: Amer Rev Resp Dis, 1959, *80*, 326.

[11] Fox, W., *et al.*: Tubercle, 1957, *38*, 71.

TABLE 1

GROWTH OF PRIMARY CULTURES FROM CONCENTRATED SPECIMENS OF PATIENTS TREATED FOR AT LEAST TWO YEARS WITH ISONIAZID

Patient		Culture Number	Amount of Growth–No Isoniazid Control (No Isoniazid)	Catalase Activity*	Amount of Growth on Agar Plates Containing Isoniazid							Dilution Factor
Number	Name				0.1 γ/ml.	1 γ/ml.	5 γ/ml.	10 γ/ml.	25 γ/ml.	50 γ/ml.	100 γ/ml.	
1	K. W.	7083	4+†	MH	4+	1+	1+	1+	1+	—	—	3
2	A. C.	6072	4+	L	4+	4+	4+	3+	3+	3+	3+	5
3	B. J.	8250	4+	L	4+	4+	4+	4+	4+	4+	4+	5
4	H. W.	8017	4+	H	4+	4+	4+	4+	4+	—	—	6
5	C. R.	8689	3+	H	3+	—	—	—	—	—	—	2
6	S. A.	9384	4+	M	4+	4+	4+	4+	3+	—	—	4
7	N. R.	8671	4+	H	4+	2+	—	—	—	—	—	3
8	S. B.	8711	4+	H	4+	4+	4+	4+	3+	1+	1+	8
9	McR. A.	8853	4+	L	4+	4+	4+	4+	4+	4+	4+	5
10	M. E.	9041	4+	H	4+	4+	1+	10 colonies	—	—	—	4
11	M. L.	8700	3+	M	3+	3+	3+	3+	3+	2+	2+	2
12	M. D.	8708	4+	L	4+	4+	4+	3+	1+	12 colonies	8 colonies	4
13	McG. J.	15680	4+	M	4+	4+	3+	1+	1+	5 colonies	5 colonies	5
14	L. A.	5686	4+	L	4+	4+	4+	4+	4+	4+	4+	4
15	M. J.	8680	4+	MH	4+	4+	3+	1+	—	—	—	6
16	McG. R.	19015	2+	M	2+	2+	2+	1+	1+	—	—	—
17	C. L.	20148	2+	M	1+	30 colonies	30 colonies	30 colonies	30 colonies	30 colonies	20 colonies	—
18	F. A.	18487	2+	M	1+	1+	5 colonies	—	—	—	—	—
19	D. M.	23259	50 colonies	M	50 colonies	50 colonies	50 colonies	50 colonies	50 colonies	50 colonies	50 colonies	—
20	C. F.	28332	3+	MH	3+	3+	2+	2+	30 colonies	—	—	2
21	K. W.	34406	20 colonies	H	20 colonies	—	—	—	—	—	—	—
22	D. A.	35773	50 colonies	M	50 colonies	50 colonies	1 colony	—	—	—	—	—
23	B. O.	38790	3+	L	2+	2+	2+	2+	2+	2+	2+	3
24	C. L.	44787	34 colonies	M	15 colonies	10 colonies	10 colonies	10 colonies	10 colonies	10 colonies	10 colonies	—
25	N. F.	45161	2+	H	2+	2+	—	—	—	—	—	—

26	G. C.	46480	4+	H	4+	4+	3+	10 colonies	—	—	—	2
27	R. M.	47677	50 colonies	H	50 colonies	—	—	—	—	—	—	—
28	B. J.	47603	22 colonies	M	20 colonies	10 colonies	10 colonies	10 colonies	3 colonies	—	—	—
29	S. S.	52269	25 colonies	H	2 colonies	—	—	—	—	—	—	—
30	B. P.	55026	2+	M	2+	2+	1+	1+	1+	1+	—	—
31	R. V.	42695	12 colonies	L	8 colonies	6 colonies	6 colonies	4 colonies	4 colonies	4 colonies	1 colony	—
32	L. H.	55081	3+	M	2+	2+	2+	2+	2+	2+	—	2
33	S. J.	58820	2+	H	2+	2+	2+	—	—	—	—	—
34	N. E.	57813	46 colonies	L	40 colonies	42 colonies	42 colonies	41 colonies	42 colonies	49 colonies	—	—
35	G. W.	60921	4+	H	4+	1+	—	—	—	—	—	3
36	H. J.	56235	14 colonies	M	10 colonies	5 colonies	—	—	—	—	—	—
37	A. J.	59354	40 colonies	H	40 colonies	25 colonies	—	—	—	—	—	—
38	K. C.	61555	2+	H	2+	2+	1+	—	—	—	—	—
39	R. W.	65598	52 colonies	H	50 colonies	50 colonies	—	—	—	—	—	—
40	G. K.	66478	4+	M	4+	4+	4+	—	—	—	—	4
41	H. A.	764	2+	H	1 colony	—	—	—	—	—	—	—
42	D. J.	8311	4+	M	4+	4+	3+	2+	2+	2+	2+	5
43	R. C.	12278	31 colonies	H	31 colonies	30 colonies	26 colonies	25 colonies	20 colonies	20 colonies	—	—
44	M. J.	15457	10 colonies	M	10 colonies	5 colonies	—	—	—	—	—	—
45	G. E.	21677	3+	M	3+	3+	2+	1+	15 colonies	—	—	—
46	J. W.	21929	4+	L	4+	4+	4+	3+	3+	3+		6

* H = high catalase activity (75–100%)
MH = moderately high catalase activity (50–75%)
M = moderate catalase activity (25–50%)
L = low catalase activity (10–25%)
There were no cultures completely inactive.

† 4+ = 350 colonies or over
3+ = 200–350 colonies
2+ = 100–200 colonies
1+ = 51–100 colonies
Less than 1+ actual count.

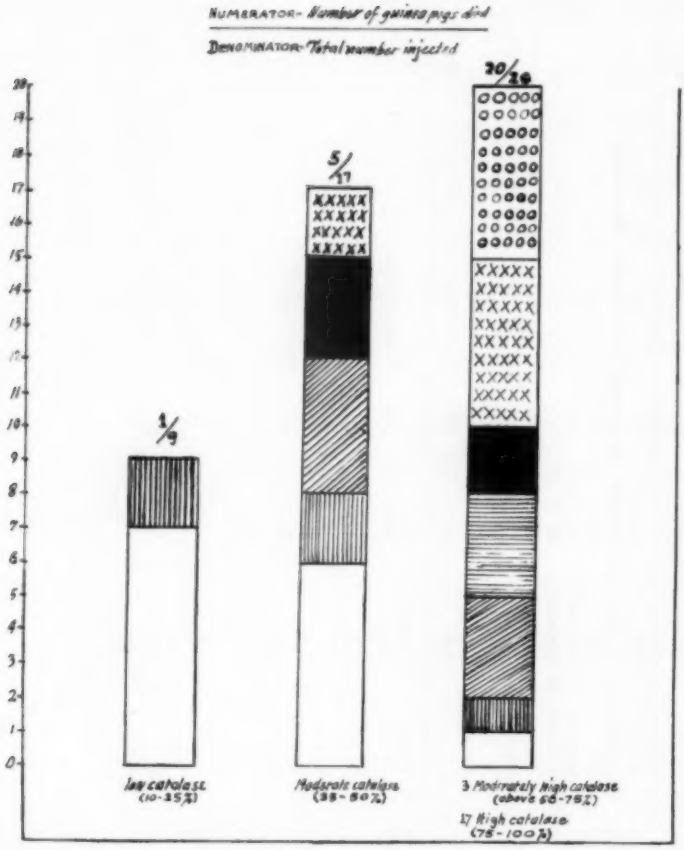

FIG. 1. Correlation of catalase activity, isoniazid resistance, and guinea pig virulence of cultures isolated from sputum of 46 patients after two years on isoniazid therapy.

Resistant to:

100 γ per ml.
50 γ per ml.
25 γ per ml.
10 γ per ml.
5 γ per ml.
1 γ per ml.
0.1 γ per ml.

tubercle bacilli isolated from a single sputum specimen of each of 46 patients who had been on isoniazid therapy for at least two years. The degree of drug resistance of these populations was remarkably diverse. Based on guinea pig virulence, the isoniazid-resistant sputum isolates seemed to fall into 5 different types of populations of tubercle bacilli.

Based on their catalase activity it was possible to group the populations of tubercle bacilli isolated from the sputum of the 46 isoniazid-treated patients into three categories irrespective of drug resistance: (*1*) those of high catalase activity which were guinea pig virulent; (*2*) those of moderate catalase activity which were or were not virulent for guinea pigs; (*3*) those of low catalase activity which were usually nonvirulent for guinea pigs.

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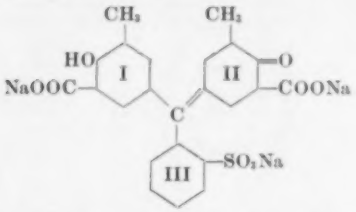
January 8, 1960

METACHROMASIA OF MYCOBACTERIA

Eriochrome® Cyanin R, Alizarol Cyanin RC, Pontachrome Blue, and half a dozen other names, indicate the aryl methane dye, CI 722 (old) or 43820 (new), mordant blue III:



As the sulfonate group indicates, it is highly water soluble, and is nearly neutral in reaction in 1 per cent aqueous solution. Even in a 5 per cent aqueous solution it fails to stain mycobacteria but, when incorporated into the Ziehl-Neelsen formula, the dye stains mycobacteria in a characteristic manner.

Mycobacterium lepraemurium has been used most extensively in this work because of the massive numbers of organisms occurring in the tissues. Paraffin sections thus become a practicality, with smears easily and quickly prepared from fresh tissue suspensions. In addition, both sections and smears of *M. leprae* have been widely used. The bovine mammalian tubercle bacillus, BCG, has been studied in smears from cultures on both simple broths and Dubos medium. *Mycobacterium tuberculosis* strain H37Rv has been used mainly for confirmation, in smears and in lesions from guinea pigs. *Mycobacterium smegmatis* was the nonpathogen most studied.

In preparation of smears, several techniques have been used: heating, gelatin and egg albumin bases, et cetera. In all cases simple smears, using no adhesive or heating, have been widely employed and, in retrospect, it can be said that heat and adhesives do not materially affect the results obtained.

Eriochrome Cyanin R dissolves readily in cold water, in alcohol, in liquefied phenol, and in most standard solvents. No difficulties are encountered in the mode of preparation of solutions, and it is heat stable. It has been used principally in the following formula:

Eriochrome Cyanin R	2.0
Phenol	5.0
Ethyl alcohol	10.0
Water, as necessary	100.0

The proportions are in no sense critical, and it is doubtful that the alcohol contributes essentially, but it has been used regularly to facilitate incorporation of added ingredients being tested.

Neutral aqueous solutions of Eriochrome Cyanin R show three absorption maxima, the most striking of which is at about 525 lambda. The "blue" maximum at about 570 lambda is weak unless the solution is mordanted or slightly alkalinized. It varies somewhat with the mordant used. There is also a broad band with an ill-defined maximum at about 420 lambda, but ranging from 410 to 430.

When smears of mycobacteria are stained in the above solution for thirty minutes and washed in tap water at pH 9.0, the bacilli are stained orange, whereas other organic matter, including other bacteria, are deep blue in color. In paraffin sections the mycobacteria show the same characteristic color. Collagen and cartilage are a smooth light blue, and nuclei a deep blue. Erythrocytes and both smooth and striated muscle fibers are stained brilliant red. The orange color of the mycobacteria is obtained without differentiation in acid, or in acid alcohol. The dyestuff does not tend to overstain any of the tissue components greatly, so that brief washing in acid-alcohol is usually unnecessary, although not harmful.

Microscopic visualization of yellow or orange bacilli is not good, even with filters. The combination of a Wratten K-1 No. 6 plus a simple blue glass may help. Preparations with abundant bacilli are almost essential, and there is no promise that these orange-colored bacilli could ever enjoy a practical usage.

Phenol chelation: Without phenol chelation the metachromasia is absent, or at best slight, because the mycobacteria remain unstained. *O*-, *m*-, and *p*-cresol, as well as catechol, may be substituted for phenol. Dimethyl phenol is moderately effective. Hydroxyhydroquinone has been observed to have some effect; but resorcinol, pyrogallol, and hydroquinone are too active chemically to be useful.

Metal chelation and mordanting: Eriochrome Cyanin R was discovered by Conzetti in 1906,[1] and is moderately used commercially for lightfast dyeing wool blue, using chrome mordants secondarily. The addition of metallic salts to staining solutions has had the same effect as that usually encountered when a metal atom is incorporated into a dye molecule. Fixed shades are produced, and the ability to stain mycobacteria is lost. Copper, uranium, and iron salts produce

[1] KRAHLER, S. E.: Miscellaneous dyes, in *The Chemistry of Synthetic Dyes and Pigments*, H. A. Lubs, ed., Reinhold Publishing Corp., New York, 1955, p. 285.

brilliant red violets and blues. Potassium dichromate as a primary mordant hastens the staining of mycobacteria slightly. However, the clear characteristic orange color is altered by the addition of some part of the blue moiety, so that all three colors potentially present in the dye may be transferred to the mycobacteria. At pH 4.0 for the dichromate mordant the orange will predominate, although even here it is possible to see poorly defined blue granular spots in the chromed and stained bacilli. More of the blue appears when buffered to pH 6.0. Sodium molybdate as a secondary mordant at pH 7.05 shows the bacilli as more blue than orange, but with some orange still clearly present. Alum, copper, and other metals interfere with the staining of bacilli. Even when a mordant, such as chromium, does show an effect, phenol chelation continues to be significant.

Sodium tungstate as a secondary mordant has been used extensively because of the uniform deep blue staining of nuclei obtained, without affecting the orange-colored mycobacteria. The nuclear chromatin is effectively and permanently blued to a color, suggesting a usefulness as a general nuclear stain, although the red coloring of hemoglobin is lost. A thirty-minute staining period is still required, and phenol chelation increases the amount of dye in nuclear material. Overstaining is easily controlled with acid-alcohol washing.

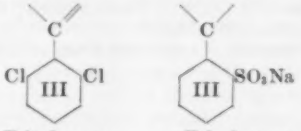
Hydrogen ion concentrations: The orange staining of the mycobacteria is remarkable for the fact that it may be elicited from pH 1.6 (0.1 N H_2SO_4) to pH 6.6. There is no sharp optimal point, which may be at about pH 5.0. The dye itself is yellow at pH 1.6, red at pH 6.6, and becomes a weak blue when slightly alkaline. It is faint yellow when strongly alkalinized. The color changes are not sharp.

Sulfonation and oxalation: The presence of the oxalate radical in the dye molecule suggested that addition of oxalates might have an effect. Small quantities do not prevent the mycobacterial staining, but prevent the blue staining of other structures. Sulfates behave similarly except that, with 0.1 N solutions, it is possible to obtain better bacillary staining than with oxalates, and some counterstaining when the solution is moderately acid (pH 3.0 to 5.0). Both sulfates and oxalates provide good definition of the mycobacteria but, in the balance, are not found useful in the study.

Variation according to species of mycobacteria: No variation has been observed. The reaction appears to be the same for all of the organisms studied. The reaction has not been observed with respect to other bacteria or fungi, or other cellular or biologic structures. The subject has not been covered specifically to eliminate all possibilities.

Mycobacterium smegmatis has shown an interesting part of the reaction. The strain employed, grown on heart-infusion broth and 5 per cent glycerin, is only moderately acid fast to the usual basic fuchsin acid-fast technique. That is, many nonacid-fast bacilli are observed. When stained with Eriochrome Cyanin R, the ratio of orange- to blue-stained bacilli is the same as the ratio of acid-fast to nonacid-fast bacilli in standard acid-fast preparations. The acid-fast bacilli stain orange; the nonacid-fast, blue.

Other dyes: Eriochrome Azurol B (Pontachrome Azure Blue B, mordant blue 1, C. I. 720 (old) or 43830 (new)) is similar structurally to Eriochrome Cyanin R:



Eriochrome Azurol B — Eriochrome Cyanin R

It differs so slightly as to suggest a similar staining reaction. However, it is much less water soluble, and in the Ziehl-Neelsen formula has no affinity for mycobacteria whatever. Only a few other dyes, such as mordant blues 29 and 55, or mordant violet 39, have configurations suggesting a possible similar reaction, but the failure with Eriochrome Azurol B does not encourage their investigation.

* * *

Two of the three axes of the molecule of Eriochrome Cyanin R (I and II in the diagram) contain a methyl group neighboring the auxochrome group para to the attachment to the methane nucleus. It is probable that the metachromasia is effected by phenol chelation within these two axes, but not the third.

The —OH and =O groups in the para positions also suggest that these axes are responsible for the yellow and red moieties of the dye, rather than the third axis. However, the marked blue color effected by mordants, and by dyeing of tissues generally, indicates a rearrangement within the molecule to produce the blue color, which is otherwise weak.

Difficulty in obtaining preparation of a sharp, clear, distinctive yellow coloring of the mycobacteria (as opposed to orange) is presumably related to the slight degree of insulation between parts I and II of the molecule. Because "the colors of most dyes vary to some degree with the type of fiber upon which they are used,"[2] it must be sup-

[2] GRAHAM, D.: Color and chemical constitution of dyes, in *The Chemistry of Synthetic Dyes and Pigments*, H. A. Lubs, ed., Reinhold Publishing Corp., New York, 1955, p. 675.

posed that the yellow-orange metachromasia is related to a specific character of the mycobacterial surfaces. The fact that it is independent of whether the organisms are derived from the tissues of infected animals or from artificial cultivation means that it is a property of the Mycobacterium rather than its environment.

The binding of neutral red in alkaline solution by tubercle bacilli, as observed by Dubos and Middlebrook,[3] with conversion of the bound dye to its red shade (acid), appears to be a different phenomenon. Similar observations of Desbordes[4] with respect to Nile blue A, with hydrolysis to the acid-red oxazone, likewise begin with absorptions from the alkaline state. Although suggestions of relationships of these responses to virulence or metabolic states have been made, the Eriochrome Cyanin R response appears purely chemical in nature. No relationship to any particular element in the mycobacteria, such as mycolic acid, is supposed.

In summary: Mycobacteria are colored a metachromatic orange by the triphenyl methane dye, Eriochrome Cyanin R.

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March 3, 1960

[3] DUBOS, R. J., AND MIDDLEBROOK, G.: Amer Rev Tubere, 1948, *58*, 698.

[4] DESBORDES, J.: Ann Inst Pasteur (Par), 1952, *83*, 809.

INVESTIGATIONS ON ANTITUBERCULOUS CHEMOPROPHYLAXIS AND COMPARATIVE TESTS WITH BCG VACCINATION

Since 1953 in the Istituto Zooprofilattico Sperimentale dell'Umbria e delle Marche, laboratory tests and investigations in the field have been carried out with the aim of studying the chemoprophylaxis of bovine tuberculosis. The results of the first laboratory experiments showed that isoniazid is effective in tuberculous infection in this host. Field studies revealed that by means of isoniazid it is possible to breed healthy calves in infected surroundings and to reclaim herds that are seriously affected by tuberculosis.

Successively, as a part of the long-term chemoprophylactic studies at this institute, more extensive experiments were carried out with the aim of studying whether chemoprophylaxis is able to strengthen antituberculous resistance.

With the aim of investigating an eventual increased resistance against tuberculosis due to chemoprophylaxis, three series of experiments have been carried out that have required the use of fifty head of cattle. A report has already been made on the first and second series of these experiments.[1] The third experiment was concluded December 5, 1959, and is reported only briefly at this time. A detailed report will be published subsequently.

These last studies were performed to clarify whether chemoprophylaxis employed on young tuberculin-positive calves by a regimen of interrupted drug administration not only protects these animals from the disease, but also strengthens their resistance. As a comparative point for the increased resistance against tuberculosis, vaccination with BCG was employed.

The experiment consisted of exposing to natural infection (contact with a cow definitely infected with "open" tuberculosis) 3 uninfected calves for a period of four months. At the first appearance of tuberculin sensitivity (two months after contact with the infected cow), a first two-month course of treatment with isoniazid (10 mg. per kg. per day) was started. At the end of the first cycle, the source of infection, i.e., the diseased cow, was removed while the 3 calves underwent a rest period of two months. A second treatment course of two months was then given, then a month of rest and, finally, a course of treatment that lasted a month.

Another group of 4 calves was vaccinated with BCG for comparative purposes; these animals were kept in an open stable during the summer.

A week after the end of the isoniazid treatment (the first group) and five months after the vaccination (the second group), the animals of both groups and 3 of the control animals were challenged with subcutaneous injections of a moist culture of 50 mg. of a virulent strain of bovine tubercle bacilli.

The infected animals were kept under continuous clinical observation (control of temperature, weight, et cetera), and very soon an evident difference could be noticed between the control animals and the calves belonging to the other two groups. In the control animals, a diseased state could be demonstrated from all of the various examinations carried out; in the drug-treated and in the BCG-vaccinated animals, except for a granuloma at the site of injection (far smaller than in the control animals), only negligible signs of disease could be detected.

On post-mortem examination, the control animals showed a generalized tuberculosis involving all of the organs and the corresponding lymph nodes; in the vaccinated and isoniazid-treated calves, either no macroscopic change could be observed, or the lesions were very small indeed.

From such clear results there can be no further doubt concerning the immunizing effectiveness of BCG, or concerning the value of antituberculous chemoprophylaxis not only in the passive sense, i.e., protection of animals exposed to contamination during the entire period of isoniazid treatment, but also in the active sense, namely, in terms of the development of immunity.

* * *

From the results of the above investigations, several considerations have arisen concerning antituberculous chemoprophylaxis in general and its possible use in the struggle against bovine tuberculosis. A very brief summary of a few of these subjects follows.

A long discussion is taking place concerning the new terminology of chemoprophylaxis. The present writers suggest the terms "passive antituberculous chemoprophylaxis" to describe the resistance acquired during drug administration, and "active antituberculous chemoprophylaxis" to indicate the development of immunity during drug administration—an immunity that persists after the drug administration has been discontinued. The present writers believe that the success of active chemoprophylaxis is due entirely to this cycle of treatment, in which periods of drug administration and drug-free intervals are alter-

[1] Rosati, T., and Badiali, L.: Riv Tubere (Roma), 1959, 7, 207.

nated, as originally introduced by Omodei-Zorini. Of importance are the considerations concerning the possibility of the application of antituberculous chemoprophylaxis in cattle and its inclusion among the plans of tuberculosis eradication in this species of animal. In this respect it should be noted that chemoprophylaxis and vaccination are not competitive in veterinary pathology, but each method has its own definite field of application.

Finally, the question arises, concerning "active chemoprophylaxis," whether the increased antituberculous resistance remains unchanged some months after the end of treatment. On the basis of some practical observations (treatment of infected herds already under control), one could answer in the affirmative. It remains to be seen how animals submitted to chemoprophylaxis react against a severe challenge carried out some months after the end of treatment. Another series of investigations of this question has already been started.

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March 15, 1960

Correspondence

EFFECTS OF CARBON DIOXIDE AND DAYLIGHT IN CULTURING TUBERCLE BACILLI

To the Editor of the American Review of Respiratory Diseases:

This communication is to emphasize the practical importance of carbon dioxide in the routine culture of tubercle bacilli and to call attention to the deleterious effect of daylight on the Middlebrook 7H-9 (or 7H-10) medium.

It seems evident that culture media cannot be evaluated without specific reference to the environment in which they are used. Comparisons of media, as performed in other laboratories (without carbon dioxide enrichment of the atmosphere under which *M. tuberculosis* is cultivated), have shown mediocre results for the 7H-9 medium.[1, 2] However, it has been demonstrated that *carbon dioxide is important* in the cultivation of tubercle bacilli and is an essential factor in the use of the 7H-9 (or 7H-10) solid medium.[3-5]

This emphasizes the importance of the techniques employed. The carbon dioxide chambers used in this laboratory are large metal storage cabinets which can be shut tightly. These are kept in walk-in incubators. When smaller incubators are employed, it should be possible to seal the ordinary air ventilation openings to prevent loss of carbon dioxide. In both cases, the gas should be introduced into the top of the chamber from commercially available 10 per cent carbon dioxide—90 per cent air cylinders—while the air in the chamber escapes through an opening near the bottom. When sufficient gas has been introduced to make the atmosphere approximately 2 to 5 per cent carbon dioxide in air, the openings should be sealed. The chamber or incubator should be opened only once daily, and carbon dioxide should be added after each opening.

Tube slants, bottles, or Petri dishes must be so handled that carbon dioxide actually can diffuse into the atmosphere in contact with the bacterial cells. To this end, tubes or bottles with screw-caps should be left for a day or two with the caps partly unscrewed. Similarly, Petri dishes and Felsen quadrant plates (or other types of plates) should be left *right-side* up in the incubator so that a moisture seal is avoided. Polyethylene plastic bags which are freely permeable to carbon dioxide but impermeable to water vapor are used to prevent drying out of the medium in Petri dishes.

The 7H-9 (or 7H-10) transparent solid medium has been used in this laboratory under 2–5 per cent carbon dioxide in air and without prolonged exposure to daylight. It has yielded an increased rate of growth, increased numbers of colonies, and decreased rate of contamination in comparison with Löwenstein-Jensen and American Trudeau Society media.[4-7]

This transparent medium has certain practical advantages. The first and most important of these is that most of the colonies of tubercle bacilli have appeared on this medium within twenty-one days. Further incubation has been shown to result merely in increased size of the colonies; the number of colonies remains essentially unchanged.[6] Thus, clinically useful results (cultures, type of mycobacteria, and specific drug-susceptibility test results) are available in three weeks. The second advantage is that this medium is transparent, permitting examination of colonies with either dissecting or stereoscopic microscopes when needed. This allows identification of very small colonies, as well as closer study of colony morphology. Furthermore, the distinctive rough colony morphology of *M. tuberculosis* as well as both rough and smooth colonies of the various "unclassified" mycobacteria are readily recognized. The third advantage of this medium is that it solidifies without inspissation. Thus, precise concentrations of various antimycobacterial agents may be added for drug-susceptibility testing without being subjected to partial inactivation by the heating necessary for the preparation of the complex egg media.

Not only is carbon dioxide enrichment an essential factor in the use of 7H-9 (or 7H-10) solid medium, but it has been shown to be *required* for the growth of certain wild strains of tubercle bacilli on egg media. One of the factors to be considered whenever sputum specimens from a patient are consistently positive for acid-fast rods on Ziehl-Neelsen-stained films of the sputum but are *con-*

[1] JEFFERIES, M. B., *et al.*: Amer Rev Resp Dis, 1960, *81*, 259.

[2] BERTE, S. J., AND TUCKER, E. B.: Amer Rev Resp Dis, 1960, *81*, 595.

[3] SCHAEFER, W. B., *et al.*: J Bact, 1955, *69*, 706.

[4] COHN, M. L., *et al.*: Amer Rev Tuberc, 1954, *70*, 465.

[5] MORSE, W. C.: Personal communication.

[6] MIDDLEBROOK, G., AND COHN, M. L.: Amer J Public Health, 1958, *48*, 844.

[7] MIDDLEBROOK, G., *et al.*: Amer Rev Tuberc, 1954, *70*, 852.

sistently negative for mycobacteria on culture is the possibility that carbon dioxide enrichment is needed.

One additional important factor pertaining to 7H-9 (or 7H-10) solid medium has recently been found. Exposure of prepared plates of this medium to bright, but indirect daylight (shielded by ordinary glass) for as short a time as thirty-six hours has resulted in a change which often completely prevented growth of tubercle bacilli from moderate or small inocula. This has also been confirmed by Morse.[5] Therefore, it should be emphasized that tube slants, bottles, and plates of these two media should be stored in the dark prior to use and should be incubated in the dark to prevent this deleterious effect.

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May 9, 1960

AN EASY METHOD FOR THE DETECTION OF PARA-AMINOSALICYLIC ACID (PAS) IN URINE

To the Editor of the American Review of Respiratory Diseases:

The necessity for a two- or three-drug regimen in the treatment of tuberculosis makes it also necessary to supervise as accurately as possible whether the patients are actually taking the drugs prescribed. For, if the patient omits one of the drugs in a two-drug regimen, he is in effect giving himself single-drug therapy. Unfortunately, because patients receiving PAS therapy sometimes feel variable degrees of discomfort, many of them discontinue this medication and frequently this occurs without their physicians' knowledge. In order to prevent this happening, several tests have been developed for the detection of PAS in the urine.[1-4]

In clinical investigations of this question, the present writer has developed a method for PAS detection which appears to be practicable and have certain advantages over the various methods cited.

The method is as follows: On a sheet of filter paper, a drop of each urine specimen to be tested is placed. After drying the paper, it is sprayed with a solution of 3 per cent ferric chloride. When the urine contains a detectable amount of PAS, a wine-red spot appears on the filter paper.

The results obtained with this technique have been compared with those obtained with the Penman and Wraith methods[2] and the Dixon, Stradding, and Wooton methods[4] and, in the writer's hands, the present method is more sensitive than the Dixon, Stradding, and Wooton method, and more specific than the method of Penman and Wraith. Moreover, it has the advantage of being easier. With this technique, the urine test for PAS can be made, using only filter paper and a sprayer with a solution of ferric chloride. Thus it is possible to employ the technique in patients being treated for tuberculosis even in remotely situated clinics. A test can be made weekly or even daily if it is advisable. In outpatient practice, the test may be made once a week, as it is usually unnecessary for the patient to come to the clinic any more frequently. When it is considered what a very small amount of urine is needed for the test, it seems reasonable to believe that the specimens could be mailed in vials similar to those used for streptomycin without too much effort or expense.

It is believed that a more effective control of the PAS component of multiple-drug therapy would result in a definite improvement in the results obtainable from the therapy of tuberculosis. Although one cannot always inform the patients that it is realized that they are not taking the PAS, the knowledge that this is so frequently allows the physician to choose the best way to resolve the individual problem with each patient.

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August 13, 1959

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[1] SIMPSON, J. D.: Tubercle, 1956, *37*, 333.
[2] PENMAN, H. G., AND WRAITH, D. G.: Lancet, 1956, *2*, 552.
[3] RUIZ, B. C.: Tubercle, 1957, *38*, 152.
[4] DIXON, W. M., STRADDING, P., AND WOOTON, I. D. P.: Lancet, 1957, *2*, 871.

Books

ELEMENTARY STATISTICS WITH APPLICATIONS IN MEDICINE AND THE BIOLOGICAL SCIENCES. By Frederick E. Croxton. Pp. 376, Dover Publications, Inc., New York, 1959. Price, $1.95.

This is an unabridged and corrected version of the work first published under the title, *Elementary Statistics with Applications in Medicine*. The present edition has a soft cover, and includes tables, graphs, an appendix of statistical tables, a subject index, and an introduction to mathematical symbols preceding each of the technical chapters.

The first chapter deals with rates, ratios, and percentages, a knowledge of which is essential to the physician if he is to have any appreciation for statistics. The second chapter also is very basic in nature. It concerns the tabular and graphic presentation of data. The physician should find this chapter extremely useful in preparing a talk or an article for publication.

The third chapter is the first of a series of chapters on basic statistical theory. Here, the concept of the frequency distribution is introduced. In Chapter 4, there is a discussion on measures of central tendency, or constants which summarize data. All parts of Chapter 5 may not prove useful to the reader. For example, the concepts of skewness and kurtosis, although of interest to the theoretician, may confuse rather than assist the reader in his understanding of statistics. The section on measures of dispersion or variability is all that is really necessary in this chapter.

Chapter 6 deals with linear correlation and regression for 2 variables. This chapter should prove quite useful, except for the section on coefficients of determination and alienation, which are of no great importance in medicine and which certainly do not lead to a better understanding of simple regression theory. Chapter 7 regarding nonlinear and multiple and partial correlation may be a bit too complex for a book on elementary statistics. At this stage, it would be sufficient simply to indicate t he practical value of these statistics. Seemingly, the techniques outlined in this chapter, even when properly applied, have proved to be of no great value in medicine or in the biologic sciences.

In Chapter 8, the author gets into some specific sampling distributions—perhaps the more essential ones—the normal distribution, the binomial, and the Poisson. This chapter must be included even in an elementary book on statistics. However, too much emphasis may have been placed on fitting these distributions to observed data, a matter which is not of vital concern to the reader.

In Chapter 9, the author discusses the sampling distribution of the mean, confidence limits for a population mean, and tests of significance for comparing a sample mean with an assumed population mean and for comparing two sample means. He does this by way of the normal distribution and then introduces the t-distribution. It is surprising that the author does not develop a basis for comparing two sample means through a consideration of the sampling distribution of the difference in means.

Chapter 10 is a logical extension of Chapter 9. It is concerned with the sampling distribution of the proportion and, to a lesser extent, the sampling distribution of the difference in proportions. A distinction is made between small and large samples in regard to approximation of the binomial by the normal distribution, but the author does not lay down any rules for ascertaining when a sample size is large enough to allow for such an approximation.

Chapter 11 is a chapter on the chi-square distribution and the various tests of significance that are related to that distribution. This chapter is essentially a generalization of Chapter 10. In essence, the reader is given a more flexible tool for comparing sample proportions.

The final chapter, Chapter 12, is effectively a catch-all for concepts not covered in earlier chapters either because the reader was not prepared for them or because they did not appear to fit elsewhere. The author considers a comparison of a sample variance with an assumed population variance by means of the chi-square test, and then introduces the F-distribution in a test for the comparison of two sample variances. This leads the way to a discussion of the analysis of variance, which is a generalization of the method for comparing sample means. At this point, it is logical and convenient for the author to show the relationship between the normal, t, chi-square, and F distributions. Finally, the author presents tests of significance for correlation and regression coefficients and for measures of skewness and kurtosis.

The chief criticism of this book is that it does not place enough emphasis on statistical hypotheses. These hypotheses form a philosophic basis for tests of significance. Many authors consider them too abstruse for a book on elementary statistics, but they are worth emphasizing and re-emphasizing to the point where they are mastered. They at least deserve more attention than the author was willing to give them. The reader will obtain a much

better appreciation for statistics that way. Mention is made of errors of the first and second kind, but the value of such information is rather limited without a more comprehensive discussion on statistical hypotheses.

All in all, this book should prove quite useful to the beginner in statistics. It is not the only book of its kind, but could easily be classified among the better ones. It is well written and not oversimplified at the expense of being unrealistic. With the exception of certain criticisms raised earlier, the subject matter is treated in such a way as to allow for a minimal amount of confusion on the part of the reader—that is, in spite of the inherent complexity of the material.

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MICROBIOLOGY YESTERDAY AND TODAY. Edited by Vernon Bryson. Pp. 122, Institute of Microbiology, Rutgers, The State University, New Brunswick, New Jersey, 1959. Price, $4.00.

Microbiology draws its resources from many different scientific and practical areas. In the past twenty years it has developed into a discipline with only vaguely defined boundaries. It has evolved into a fundamental biologic science, has contributed to modern biochemical thinking, and has furthered practical developments in the field of industry, medicine, and public health. It is almost impossible for a single individual to foresee from his vantage point in which directions future investigations will lead microbiology. Reading the title of the present publication, one would expect some help in this direction, since consideration of the past and the present naturally points toward the future. However, this is not the case. As much merit as single contributions to this volume might have, the book as a whole does not carry any strong message. These contributions might have been very valuable when presented during the symposium that this book commemorates (held in honor of the seventieth birthday of Selman A. Waksman), but the reader misses in them originality either factually or conceptually.

There are two contributions which deserve mention, one by Heidelberger and the other by Cowan. The first is an account of personal trials and tribulations in the field of immunology, and brings to light relatively little-known investigations by the author. The second contribution, by Cowan, arouses sympathetic reactions when he points to the weaknesses of our present-day taxonomic system in microbiology. Using the products of the Ford Company as his example, he shows that our concepts of genus and species are based on relative values and not on absolute ones, and that we make them what we want them to be.

After having read this book, one wonders about the wisdom of having too many "presses" which are willing to print books without regard for the prospective reader.

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L'EXPERTISE DE LA SILICOSE PULMONAIRE. By Paul Sadoul and Maurice Dusapin. Pp. 234, Masson & Cie., Paris, 1959.

This very informative book does not concern itself with "expertness" in the field of silicosis, nor is it merely a "review" of knowledge concerning silicosis. Rather, the translation of the title should be "The Evaluation of Cases of Pulmonary Silicosis," for purposes of compensation.

Toward this end the book is divided into sections: the first dealing with the development of compensation laws in France; next, a series of chapters describing the reasoning and compensation actions of one regional board of evaluating physicians; and, finally, a direct quotation of the "legal text concerning silicosis." The book was written by two members of the Regional College of Three Physicians of Nancy, which is one of several such groups established in various parts of France. These "colleges" are directly comparable to the so-called Silicosis Referee Boards charged with the responsibility of diagnosing and recommending compensation of individuals with various pneumoconioses in certain states of the United States.

As one reads this book the impression is gained that the "College of Nancy" is extremely liberal in awarding compensation to industrial personnel. In fact, a statement on pages 82 and 83 in the chapter concerning "uncomplicated silicosis" (simple nodular silicosis) expresses their point of view succinctly: ". . . any (pulmonary) incapacity is entirely attributed to occupational disease if the latter is radiologically demonstrable."

This concept indicates that the writers believe that simple silicosis can cause pulmonary insufficiency, and that any change observed cannot be distinguished from any that might have occurred whether or not the individual concerned had been exposed to dust. The evidence upon which this belief is based is presented in the book and seems extremely tenuous to this reviewer. Since this

concept is at variance with generally accepted views among students of the problem in this country, it seems necessary to comment upon the evidence and reasoning responsible for it.

The evidence quoted (page 80) is a pathologic investigation based upon 2,358 autopsies which revealed "severe emphysema" in 11 per cent of 88 white collar workers, 11 per cent of 511 above-ground laborers, 24 per cent of 852 miners without silicosis, and 37 per cent of 907 persons with silicosis "of whatever degree." Unfortunately, the anatomic criteria for severe emphysema are not stated; however, it is noted that "emphysema and chronic bronchitis have not been separated." In further discussion of this matter, the writers remark that "the (clinical) consequences of these emphysematous lesions are only rarely very marked," and they give a figure, based on functional tests, of only 5 per cent "severe emphysema" among silicotics of *all stages*. To this reviewer it is not logical to conclude from this that simple silicosis can produce manifestations of pulmonary insufficiency. Logic suggests that any instances of simple silicosis in the 5 per cent group were in men destined to have pulmonary insufficiency whether or not they breathed dust.

Other details of the attitudes of the French workers toward pneumoconiosis, functional tests, and compensation are also of great interest. For example, they use most of the familiar function tests, including maximal breathing capacity, maximal expiratory flow rate, and residual volume determination. In addition, they describe other procedures such as the expression of treadmill exercise data in terms of work accomplished in watts rather than merely the rate and angle of the treadmill.

Several pages of the book are devoted to a discussion of "siderosis," including its roentgenographic, functional, and pathologic aspects. Fibrosis and nodule formation are described. Since these phenomena are not generally considered to occur in siderosis in the United States, it is of interest to note that the cases so diagnosed in France are in iron miners, who are not exposed to pure iron oxide but to a mixture of mine dusts including silica. The entity called siderosis in the book would be termed siderosilicosis here.

At any rate, the observations upon which opinions and practices of pneumoconiosis compensation medicine in France are based are well and fully presented in this book. The reader can evaluate the evidence for himself if he so desires. The bibliography is of great value and includes some 173 papers extending through 1958. It covers primarily the recent European literature concerning the pneumoconioses.

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Columbus, Ohio

BOOKS RECEIVED

CLINICAL ELECTROCARDIOGRAPHY. By Robert P. Grant. Pp. 225, McGraw-Hill Book Company, Inc., New York, 1957. Price, $7.50.

CLINICAL PHYSIOLOGY. The Functional Pathology of Disease. Edited by Arthur Grollman. Pp. 854, McGraw-Hill Book Company, Inc., New York, 1957. Price, $10.00.

THE PRACTICAL EVALUATION OF SURGICAL HEART DISEASE. By Robert G. Trout. Pp. 132, McGraw-Hill Book Company, Inc., New York, 1959. Price, $10.00.

PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON IMMUNOLOGY. (Comptes-Rendus Symposium International D'Immunologie.) Pp. 450, International Committee for Microbiological Standardization, Opatija, Yugoslavia, 1959.

THE OFFICE ASSISTANT. In Medical Practice. By Portia M. Frederick and Carol Towner. Pp. 407, W. B. Saunders Company, Philadelphia, London, 1960. Price, $5.25.

RADIOLOGISCHE EXPLORATION DES BRONCHUS. By S. Di Rienzo and H. H. Weber. Pp. 281, Georg Thieme Verlag, Stuttgart (Intercontinental Medical Book Corp., New York), 1960. Price, $12.85.

SCIENTIFIC COMMUNICATIONS. Volume VIII A, Disipal Colloquium 1959. By the Research Department, N. V. Koninklijke Pharmaceutische Fabrieken. Pp. 76, Brocades—Stheeman & Pharmacia, Amsterdam, The Netherlands, 1960.

The Award of the Trudeau Medal for 1960

The Trudeau Medal for 1960 was awarded to Dr. Arnold R. Rich at the annual meeting of the National Tuberculosis Association, held in Los Angeles, California, May 15–20, 1960

The presentation was made by Dr. Edith M. Lincoln

DR. LINCOLN: It is customary in presenting the Trudeau Medal to conceal the identity of the recipient for as long as possible, at the same time describing the highlights in his career. In the case of this year's medallist I find this very difficult. I can perhaps tell you that he was born and received his early education in the South without revealing his identity, but the moment I mention his long and illustrious career as a teacher and investigator, culminating as Professor of Pathology in Johns Hopkins University, you know that I am speaking of Arnold Rice Rich. Merely to enumerate his accomplishments would take more time than is allotted for both presentation and acceptance of this medal and I would not want to deprive you of hearing Dr. Rich although, being a modest man, I am sure he would welcome such an occurrence.

Most of us accept as gospel Dr. Rich's basic work on the dissociation of hypersensitivity from immunity. Yet for many years this idea was regarded as heresy not only in this country but abroad. A series of lucid papers finally overcame the resistance to this fundamental concept.

Dr. Rich's studies on the nature of allergy as revealed by tissue cultures first published almost thirty years ago were guideposts to the study of the pathogenesis of tuberculosis, and his classic work on the pathogenesis of tuberculous meningitis has been the foundation of our knowledge of the evolution of this complication. Once therapy became available this concept suggested the necessity for prolonged treatment of tuberculous meningitis in children and thus heralded the conquest of the most dreaded complication of tuberculosis.

All of us interested in tuberculosis have read and reread Dr. Rich's book on the pathogenesis of tuberculosis. It has been translated into many languages and remains one of the most popular texts for medical students and house staff. I can attest to this when I think of the many times I have had to replace this book in my reference library at the hospital.

Dr. Rich has recently retired and is now Emeritus Professor of Pathology at Hopkins. Emeritus is a title in name only as he is continuing at the request of his successor as an active member of the teaching and working staff of the department.

The National Tuberculosis Association honors itself by bestowing its Trudeau Medal on a man who has made an outstanding contribution to the understanding of the pathogenesis of tuberculosis, Arnold Rice Rich.

DR. RICH: I value very highly, and warmly appreciate the honor of your regard, which this beautiful and distinguished medal represents. There is, of course, no higher recognition that a student of tuberculosis can receive from those in this country who are devoted to the study of this remarkable and beautiful, though distressing and deplorable, disease. I use the word "beautiful" deliberately and with the conviction that I shall be understood by this audience; for among those who have devoted years to the study of tuberculosis, there must be few indeed who have not grown to feel the beauty and fascination of the varied lesions and orderly processes of this complex disease, and of the problems that it presents.

Tuberculosis, in so many of its aspects, still remains mysterious after nearly a century of prodigious effort to understand it. It is possible that the eradication of the tubercle bacillus in this country, or at least the reduction of the disease to a position of only slight importance among the problems of public health, may come to pass within a reasonable period of time if action such as that embodied in the wise recommendations of the Arden House Conference can be faithfully and vigorously followed, and if there occur no disrupting catastrophes caused by Nature or by the unwise actions of men. It would be unfortunate, however, if the promise that tuberculosis may cease to be a public health problem of importance here should dampen the ardor of investigative efforts before our understanding of the disease is brought nearer to maturity.

The solution of many of the problems of tuberculosis would undoubtedly illuminate important problems relating to other diseases; but apart

from that consideration, tuberculosis itself is, of course, still a full-scale scourge in various other countries, which include some of the most populous areas of the world. In those countries the problem of reducing the disease to the status of a minor public health concern is a far more formidable problem than here; for in those countries living conditions, which are so very important in the control of tuberculosis, do not approximate the level of those with which we have been familiar in the United States. The progressive improvement in living conditions in this country was undoubtedly the main cause of the spectacular decline in the death rate from tuberculosis by 84 per cent during the fifty years immediately *before* any effective antituberculosis drug had been discovered.

The danger of a progressive increase in drug-resistant strains of tubercle bacilli in areas where antituberculosis drugs are widely used is at present regarded as more serious by some than by others; but if any such threat to the long-range suppression of tuberculosis exists (and I tend to agree with those who believe that it does exist), that danger is multiplied many times in populations in which tuberculosis is still rife. It would, of course, be extremely desirable to possess an effective drug to which the tubercle bacillus cannot become resistant and, for use in appropriate situations, a standardized vaccine or extracted antigen that can elevate resistance against the infection. But it would also be highly desirable to understand much more than we do about the nature of the bacillus and the defenses of the host, as a protection against possible future conditions in which such knowledge could be needed to prevent a resurgence of the ascendancy of the tubercle bacillus.

There will, of course, be no premature complacency among the members of this Association, but public lethargy and overconfidence, arising from the dramatic effects of the discovery of drugs active against the tubercle bacillus could destroy some of the best hopes that we have for the long-range future of tuberculosis control throughout the world.

Allow me to express again my very deep appreciation of the high honor that you have given me. Dr. Lincoln, it was a very great pleasure to receive this medal from you, for I have long admired from a distance your scientific attitude and your fine and valuable studies on tuberculosis.

NECROLOGY

Geronimo H. Alvarez, Buenos Aires, Argentina
Ruben M. Anderson, Hackensack, New Jersey
Richard R. Bartels, Albuquerque, New Mexico
John W. Berry, Albuquerque, New Mexico
William A. Bridges, Lutherville, Maryland
Lauren F. Busby, Santa Barbara, California
Guy E. Calonge, La Junta, Colorado
William J. Carroll, Middleton, Massachusetts
Manley B. Cohen, El Paso, Texas
Theodore Cooper, Baltimore, Maryland
Darcy R. W. Cowan, North Adelaide, Australia
Frank A. Craig, Haverford, Pennsylvania
Basil Cuddihy, Montreal, Canada
Michael A. Cunningham, Beaumont, Texas
Frederick I. Dessau, Pearl River, New York
Howard K. Edwards, Miami, Florida
Reuben J. Erickson, Santa Fe, New Mexico
Duncan D. Ferguson, London, Canada
John H. Fountain, Seattle, Washington
William M. Garrison, Silver Spring, Maryland
William H. Gordon, Detroit, Michigan
Robert H. Hackler, Washington, North Carolina
Prescott T. Hill, Providence, Rhode Island
Aaron Himmelstein, New York, New York
Ralph Horton, Oneonta, New York
Nathan B. Jaffe, New York, New York
So Jabro Jamada, Los Angeles, California
John C. Jones, Cresson, Pennsylvania
John T. Kalish, Baltimore, Maryland
Virgil L. Kelly, Bluefield, West Virginia
Alfonso MacDowell, Rio de Janeiro, Brazil
David Marcus, Tucson, Arizona
C. Howard Marcy, Pittsburgh, Pennsylvania
Charles H. Miner, Wilkes-Barre, Pennsylvania
Louis A. Mitchell, Newark, Ohio
Julian A. Moore, Asheville, North Carolina
Louis C. Morris, Chicago, Illinois
Keisuke Murao, Kasumi-Mura, Kashima-gun, Ibaraki-ken, Japan
James B. Nicholls, Windsor, North Carolina
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Alexander Plitas, Cullen, Maryland
Frank D. Rossomondo, New York, New York
Eugene C. de Savitsch, London, England
Louis H. Senteff, St. Petersburg, Florida
Sidney A. Slater, Worthington, Minnesota
Thomas H. A. Stites, Nazareth, Pennsylvania
James H. Stygall, Indianapolis, Indiana
Ernest Teller, Chicago, Illinois
Paul Vaksvik, Oslo, Norway
William V. Vindzberg, Wallum Lake, Rhode Island
George G. Wagner, Jr., Gowanda, New York
Redford A. Wilson, Tucson, Arizona
Lawrence E. Wood, Kansas City, Missouri

NOTICES

The following dates and locations of the next four annual meetings of the National Tuberculosis Association and the American Thoracic Society have been selected and approved:

1961—Cincinnati, Ohio—May 21–26
1962—Miami Beach, Florida—May 20–25
1963—Denver, Colorado—May 12–17
1964—New York, New York—May 24–29

1961 ANNUAL MEETING OF THE AMERICAN THORACIC SOCIETY

INVITATION

The Medical Sessions Committee *INVITES SUBMISSION OF PAPERS* on all scientific aspects of tuberculosis and nontuberculous respiratory and cardiopulmonary diseases for presentation at the *1961 ANNUAL MEETING IN CINCINNATI, OHIO, MAY 22–24.*

ABSTRACTS

(*1*) Abstracts of papers to be offered for presentation should be submitted before January 7, 1961 to the Chairman of the Medical Sessions Committee. *EIGHT COPIES* are required for distribution to committee members.

(*2*) Abstracts should be limited to a 300-word summary including *IMPORTANT DATA AND CONCLUSIONS*. Charts and tables should be attached to aid in the selection of papers. Abstracts selected for presentation at the Annual Meeting will be published in THE AMERICAN REVIEW OF RESPIRATORY DISEASES.

(*3*) Reports of interesting or unusual cases will be considered for inclusion in case conferences.

(*4*) The names, academic degrees, titles, and complete addresses of the senior author and co-authors should be included in each abstract.

(*5*) All abstracts will be reviewed by the Medical Sessions Committee. Selection will be largely based on the areas of interest suggested by you and others receiving this invitation.

(*6*) Authors will be notified by February 20, 1961, if their papers have been accepted for presentation.

(*7*) Papers presented at the Annual Meeting must be *ORIGINAL* contributions *NOT PREVIOUSLY PRESENTED OR PUBLISHED*. Medical papers presented at the meeting may be submitted to THE AMERICAN REVIEW OF RESPIRATORY DISEASES by the author if he so desires.

SUGGESTIONS

The Medical Sessions Committee is particularly anxious to build the 1961 program around your special interests. A memorandum suggesting subjects and speakers would be welcome and should be sent to the Chairman.

L. H. Schmidt, Ph.D., *Chairman*
Medical Sessions Committee
American Thoracic Society
1790 Broadway, New York 19, N. Y.

NATIONAL TUBERCULOSIS ASSOCIATION FELLOWSHIPS

As the Medical Section of the National Tuberculosis Association, the American Thoracic Society (formerly the American Trudeau Society) provides fellowships and traineeships for the graduate education of investigators and teachers in the field of respiratory diseases and tuberculosis. The following types are offered:

Edward Livingston Trudeau Fellowships: A few fellowships at a higher level of training and award are offered to specially qualified candidates with an M.D. degree who have been assured of a continued teaching or research appointment upon completion of training. Trudeau Fellowships are awarded for one year, but may be renewed up to a total period of four years.

Research Fellowships: Postdoctoral fellowships are offered to candidates holding the degree of M.D., Ph.D., or Sc.D. for further training as scientific investigators.

Predoctoral fellowships are offered to graduate students with a bachelor's degree to work on a research project for an advanced degree other than M.D.

Teaching Traineeships: Physicians entering their second or third year of residency in Internal Medicine or Thoracic Surgery at a medical center who may be interested in a career of medical teaching are offered traineeships toward that end. Supplementation of these awards by the institution involved is not necessary.

Each applicant for an NTA fellowship or traineeship must have been accepted by the head of the department under whom he expects to work for the next academic year in this country. Awards are determined by individual circumstances and are paid directly to the Fellow on a quarterly basis. They are granted for one year, beginning on any date after April first, and are renewable for a total of three years.

All applications must be submitted by November 1st. Further information about Fellowships may be obtained upon request from:

Director of Medical Education
American Thoracic Society
1790 Broadway
New York 19, New York

COURSE IN LABORATORY METHODS IN THE DIAGNOSIS OF TUBERCULOSIS

In cooperation with the Division of Special Health Services, Public Health Service, the Microbiology Laboratories of the Communicable Disease Center, Atlanta, Georgia, will offer a course in Laboratory Methods in the Diagnosis of Tuberculosis on the following dates:

October 31–November 11, 1960
January 30–February 10, 1961

This course is open to all grades of employed laboratory personnel who are approved by their State Health Officers. Practical laboratory training in all phases of tuberculosis bacteriology, including preparation of culture media, microscopy, cultural procedures, diagnostic use of animals, cytochemical techniques, and testing of drug susceptibility will be included. Demonstration and training in techniques for the isolation and identification of unclassified acid-fast bacilli will also be presented.

Laboratory directors and senior laboratory staff members may also make application for this course. No tuition or laboratory fees are charged. Reservations for this course should be made well in advance. Application forms may be obtained from the Laboratory Branch, Communicable Disease Center, Public Health Service, Atlanta, Georgia.

POSTGRADUATE COURSES ON DISEASES OF THE CHEST

Two postgraduate courses on diseases of the chest have been announced by Dr. J. Winthrop Peabody, Sr., Washington, D. C., Chairman of the Council on Postgraduate Medical Education of the American College of Chest Physicians.

The first, the 15th annual course, Clinical Cardiopulmonary Physiology, has been arranged under the co-chairmanship of Dr. Albert H. Andrews, Associate Clinical Professor of Bronchoesophagology, University of Illinois College of Medicine; and Dr. Edwin R. Levine, Assistant Professor of Clinical Medicine, Chicago Medical School. This course will be held at the Sheraton Towers Hotel, Chicago, October 24–28, 1960.

The second, the 12th annual course, Recent Advances in the Diagnosis and Treatment of Diseases of the Heart and Lungs, was arranged under the co-chairmanship of Dr. Edgar Mayer, Clinical Professor of Medicine, New York University Postgraduate Medical Center; Dr. Alfred S. Dooneief, Lecturer in Medicine, Columbia University College of Physicians and Surgeons; and Dr. Emil A. Naclerio, Chief, Thoracic Surgical Services, Harlem and Columbus Hospitals, New York City. This course will take place at the Park Sheraton Hotel, New York City, November 14–18, 1960.

Tuition for each five-day course will be $100 including round-table luncheon discussions. Additional information may be obtained by writing to: Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

THE AMERICAN REVIEW
OF RESPIRATORY DISEASES

Clinical and Laboratory Studies of Tuberculosis and Respiratory Diseases

ABSTRACTS

Edited by EDWIN D. KILBOURNE
Editorial Assistant: TERRI MANN

VOLUME 82 | October 1960 | ABST. No. 4

The Editor recognizes the inevitable incompleteness and arbitrary selectivity of any abstracting service, including this one. It is his belief that the usefulness of the present Abstracts section will be enhanced if the reader is informed of the general purpose of the abstracts and the criteria employed in their selection.

It is the purpose of the Abstracts section to acquaint the diversified and international readership of the REVIEW with the gist of original and scientific articles which are related to the general subjects of tuberculosis or respiratory diseases implicit in the title of the journal. In this connection, 42 abstracters systematically review 239 journals which represent 36 countries and which are published in 22 languages. In most instances, abstracters cover journals in fields of their special competence. It is evident that the diverse interests of the readers of the REVIEW dictate a balanced selection of clinical, laboratory, and epidemiologic studies. Such selection will often preclude the publication of articles equal in scientific merit to many presented here.

In the publication of abstracts, cognizance is taken of the extent to which the journals yielding them are circulated. Articles from journals of wide circulation may be mentioned by title only. This space-saving device is also employed for articles which defy condensation without the omission of essential data or discussion. The attention of readers is thus directed to the existence of papers which are no less important because they are not summarized.

(Requests for further information on abstracted articles should be directed to the author of the article at the address indicated by an asterisk (*) in each abstract title.)

ABSTRACTERS

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NONTUBERCULOUS THORACO-PULMONARY DISEASE

Actinomycosis and Nocardiosis. J. PEABODY* and J. SEABURY. *Amer J Med*, January, 1960, 28: 99–115. (*Washington, D. C.)

Actinomycosis and nocardiosis are closely related and often clinically indistinguishable diseases; chronic pleuropulmonary involvement, subcutaneous abscesses, and multiple draining sinuses typify both. Nevertheless, they possess too many essential differences to be considered as anything but two separate and distinct diseases. Especially important is the difference in therapy. Stated in the most elementary fashion, if one chooses to treat with penicillin all diseases caused by branching, fragmenting, filamentous fungi, then most patients with actinomycosis will recover, while almost all patients with nocardiosis will die. *Actinomyces bovis* is extremely susceptible to penicillin, and for actinomycosis this constitutes the treatment of choice. *Nocardia asteroides*, the cause of most cases of systemic nocardiosis, is a relatively resistant organism, much less likely to be eradicated by indiscriminate drug administration. Sulfadiazine exhibits greater *in vitro* effectiveness, and provides the best animal protection. More important still, its use in clinical nocardiosis has proved life-saving and has been responsible for practically every clinical recovery. The broad-spectrum antimicrobials and streptomycin show a less marked and more variable inhibitory effect. Because of the extremely serious implications of most nocardial infections, sulfadiazine is probably best combined with whatever drug appears most effective *in vitro*. Regardless of susceptibility tests, however, sulfadiazine should constitute the one essential component of any drug regimen for nocardiosis.

Basically, both actinomycosis and nocardiosis—like tuberculosis—are chronic diseases, and a dramatic response to therapy should not be expected. In both diseases, the earlier treatment is instituted, the greater the chance for cure. Chemotherapy must be continued in high dosage for prolonged periods if relapse is to be prevented. The judicious use of surgical procedures such as drainage and resection is likewise indispensable in certain cases.—T. H. NOEHREN

Coexistent Addison's Disease and North American Blastomycosis. R. FISH*, T. TAKARO, and M. LOVELL. *Amer J Med*, January, 1960, 28: 152–155. (*V. A. Hosp., Atlanta, Georgia)

North American blastomycosis, a chronic granulomatous disease caused by *Blastomyces dermatitidis*, is characterized clinically by either cutaneous or systemic manifestations. Clinicopathologic studies indicate that both forms of the disease, with the exception of the direct inoculation type of cutaneous blastomycosis, follow a primary pulmonary infection. In addition to the lungs and the skin, the genitourinary system, the central nervous system, the skeletal system, and other organs may be involved. The clinical course is reported of a patient with proved systemic blastomycosis in whom Addison's disease developed. Since the incidence of involvement of the adrenals with blastomycosis is appreciable at autopsy (between 5 and 10 per cent), this possibility should be considered in patients with systemic blastomycosis whether or not they are symptomatic, and appropriate studies should be undertaken to evaluate the adequacy of adrenal cortical function.—T. H. NOEHREN

The Pleural and Pulmonary Complications of Rheumatoid Arthritis. A. HORLER* and M. THOMPSON. *Ann Intern Med*, June, 1959, 51: 1179–1203. (*Royal Victoria Infirmary, Newcastle upon Tyne, England)

One hundred and eighty patients (52 males and 128 females) with rheumatoid arthritis who were seen during a period of 2 years were investigated for possible pleural and pulmonary lesions. Nine were found to have, or to have had, a pleural effusion for which no cause could be found other than rheumatoid disease. Eight of these patients were males. One further patient had roentgenographic evidence of a "honeycomb lung." The case histories of these 10 patients are presented. It is concluded that pelural effusion occurs not infrequently in the course of rheumatoid arthritis, predominantly in males. It may be associated with parenchymatous pulmonary disease, but more commonly occurs as an isolated finding, and then is often an inaugural event in the disease. Rheumatoid arthritis merits a place in the differential diagnosis of pleural effusion, especially when this occurs in middle-aged men and is associated with recent or developing joint symptoms (after authors' summary).—T. H. NOEHREN

Anomalous Bifurcation of the Bronchi. II. (in Japanese). K. SATA*, S. WATANABE, S. NAGAI, N. MAEDA, S. TAGA, and K. TAKEUCHI. *Clin Resp Org*, March, 1960, 15: 169–178. (*Inada Noborito Hosp., Tokyo, Japan)

The writers found 16 cases of anomalous bifurcation of the bronchi among 889 cases subjected to bronchographic examinations from March, 1956, to April, 1959. They found 183 cases of anomalous bronchial bifurcation reported by 74 writers in Japan, and classified the total of 199 cases into

the following 5 categories according to the model of Haga: diverticulum, 9 cases (8 on the right side); absence of a certain bronchus, 6 cases (4 on the right side); excessive number of bronchi, 33 cases (30 on the right side); bifurcation at an unusual site, 23 cases (19 on the right side); other abnormalities of bifurcation, 128 cases (112 on the right side). The mean incidence of abnormal bronchial bifurcation was 0.57 per cent (93 of 16,450 examinations).—I. TATENO

Etiology of Broncholithiasis. L. WEED* and H. ANDERSEN. *Dis Chest*, March, 1960, 37: 270–277. (Mayo Clinic, Rochester, Minnesota)

Calcified granulomas of the pulmonary parenchyma have, until recent years, been considered to be most likely the result of infection with tubercle bacilli. The inference has been that broncholiths originating in lymph nodes adjacent to the bronchial tree had the same etiologic basis. There has been no direct bacteriologic confirmation of such an etiologic factor in stains. By special stains and reliable culture techniques, 12 broncholiths from 9 patients were examined. Bodies with the morphologic features of *Histoplasma capsulatum* were demonstrated in stains from 5 patients. Filaments compatible with *Nocardia asteroides* were defined in 8 stains from 5 patients. In 2 stains (2 patients), structures resembling both Histoplasma and Nocardia were present in generous numbers. Coccidioides might also be expected to be found in broncholiths obtained from patients residing in areas where this organism is prevalent.—E. A. ROUFF

Infection Due to Chromobacteria. Report of a Case of Pneumonia Due to *Chromobacterium Prodigiosum* Successfully Treated with Kanamycin. L. A. BERNARD* and W. C. SUTTON. *AMA Arch Intern Med*, February, 1960, 105: 311–315. (*Hermann Hosp., Houston, Texas)

It is increasingly important to recognize the group of chromobacteria as potential causes of serious and fatal infection, particularly since the advent of the widespread use of antimicrobial agents capable of altering the bacterial flora of the human body, setting the stage for enhanced invasiveness and virulence on the part of these bacteria. Chromobacteria are capable of producing human infection ranging in severity from minor skin and respiratory infections to overwhelming and fatal septicemia. A high degree of discretion is indicated in the use of antimicrobials when instrumentation of the genitourinary tract is contemplated. The second most frequently involved organ system is the respiratory tract, with the production of a stubborn tracheobronchitis and occasionally a severe and even fatal pneumonia. The pneumonia may be more or less chronic in nature, with little or no acute symptomatology. A case of pneumonia due to *Chromobacterium prodigiosum* subsequent to a pulmonary infarction resulting from a septic embolus is presented. The infection was successfully treated with kanamycin.—W. J. STEININGER

Papilledema in Patients with Severe Pulmonary Emphysema. H. MILLER*, J. BASTRON, and T. KEARNS. *Dis Chest*, March, 1960, 37: 350–355. (*Mayo Clinic, Rochester, Minnesota)

Papilledema in association with severe pulmonary insufficiency is usually an ominous prognostic sign. Common features of reported cases have included emphysematous changes alone or associated with chronic asthma, bronchitis, or fibrosis. Impaired intrapulmonary mixing of gases has been of such severe degree as to lead to both hypoxia and carbon dioxide retention. Frequently, polycythemia, cor pulmonale, and congestive failure have also been present. Papilledema is apparently one of the most extreme and unusual signs of the adverse effects of severe pulmonary insufficiency on the central nervous system.
—E. A. ROUFF

Chronic Diffuse Interstitial Fibrosis of the Lungs. J. G. SCADDING*. *Brit Med J*, February 13, 1960, No. 5171: 443–450. (*Brompton Hosp., London, England)

Twenty-six cases of chronic diffuse interstitial fibrosis of the lungs have been observed during a period of 9 years. The clinical, roentgenographic, and physiologic features are described, and an account of morbid histology based upon studies in 13 cases is given. The prognosis is discussed, and the effects of corticosteroid treatment in 12 cases are described (after author's summary).
—E. A. RILEY

Primary Pulmonary Histiocytosis X. P. NADEAU*, H. ELLIS, JR., E. HARRISON, and R. FONTANA. *Dis Chest*, March, 1960, 37: 325–339. (*Mayo Clinic, Rochester, Minnesota)

During the past 30 years, 3 previously unrecognized disorders of the reticuloendothelial system have been described: Letterer-Siwe's disease, Hand-Schüller-Christian disease, and eosinophilic granuloma. The opinion now prevails that these 3 disorders are fundamentally related, the characteristic pathologic feature of each being the infiltration of tissue by large numbers of histiocytes. For this reason the term "histiocytosis X" has been proposed to encompass all 3 disorders. It has been known for some time that histiocytosis X may have its origin in an organ or organic system other

than the lung, and that it may involve the lung later during the course of dissemination. More recently, a number of cases have been reported in which the disease apparently originated in the lung. The term "primary pulmonary histiocytosis X" seems appropriate to encompass the formerly used terms eosinophilic granuloma of the lung and primary pulmonary eosinophilic granuloma.

Primary pulmonary histiocytosis X is a disease of unknown etiology occurring more frequently in men than in women, and is characterized pathologically by interstitial histiocytic infiltration and destruction of the lung parenchyma. In general, the symptoms, physical signs, and laboratory data are of little diagnostic value. Roentgenograms of the chest show diffuse reticulonodular pulmonary fibrosis associated with numerous small cystic areas (the "honeycomb lung"). Evidence of spontaneous pneumothorax or diabetes insipidus should point strongly to the presence of this condition, as they are the most frequent complications. A positive diagnosis can only be established by lung biopsy, and a word of caution is here indicated in that the biopsy specimen should be a fairly large-sized one.

The clinical course of primary pulmonary histiocytosis X is both variable and unpredictable. As a rule, the disease runs a wild and chronic course with a tendency toward remission. However, at times it may progress relentlessly to the point of severe pulmonary fibrosis, cor pulmonale, and congestive failure. At this time, corticosteroids given early in the course of the disease would seem to be the treatment of choice.
—E. A. Rouff

Pulmonary Cytomegalic Inclusion Disease in an Adult. T. H. Capers* and D. Lee. *Amer J Clin Path*, March, 1960, 33: 238–242. (*VA Hosp., Dallas, Texas)

An example of cytomegalic inclusion disease in the lungs of an adult, the 20th on record, is described. Evidence on the pathogenesis of this disease is conflicting, but most indications are that it is probably viral in origin.—E. Dunner

Basic Questions in the Development and Therapy of Chronic Suppurative Diseases of the Lungs (in Russian). V. I. Strutchkoff*. *Groud Khirurgiia*, January–February, 1960, 1: 64–67. (*Med. Institute, Moscow, U.S.S.R.)

The increasing number of patients with chronic suppurative diseases of the lungs is, in the author's opinion, a result of the increasing use of antimicrobials. Years ago, pneumonia gave a high percentage of mortality, which today is close to zero. Many ex-pneumonia patients have as sequalae anatomic and physiologic changes in the lung tissue and bronchi, and are candidates for chronic suppuration. The scars around abscesses result in pneumonosclerosis. Conservative treatment with antimicrobials gives only temporary improvement, but does not prevent relapse. Early surgery is advocated.

The author believes that chronic suppurative diseases may be classified as follows: (*1*) primary bronchiectasis, (*2*) chronic, nonspecific interstitial pneumonia, (*3*) chronic lung abscess, (*4*) infected cysts, (*5*) mycotic suppuration. Of 386 patients with chronic pulmonary suppuration treated by resectional surgery, the mortality was 3.1 per cent. (Pneumonectomy resulted in 5 per cent mortality, lobectomy in 2 per cent, and segmental resection in none.) Right pneumonectomy resulted in a mortality rate twice as high as that from left pneumonectomy. After surgery, 80 per cent of the patients were able to return to work.
—M. Komarjanski

Benign Superior Mediastinal Syndrome. W. R. Murdoch* and W. Will. *Scot Med J*, January, 1960, 5: 37–41. (*Royal Infirmary, Glasgow, Scotland)

Two cases are described of benign obstruction of the superior vena cava. The first occurred in a woman who first presented at the age of 41 with dyspnea and distended veins on the chest wall. She was followed for 20 years. Bilateral simultaneous venography showed complete venous block in both axillae. The venous return was carried by the intercostals and dilated collaterals. The second case was in a child of 15 who presented with sudden swelling of the face and neck. She had raised venous pressure on the neck. There was no evidence of mediastinal tumor. A venogram showed a complete block of the superior vena cava at the level of the third thoracic vertebra. The patient had positive Wassermann and Kahn reactions (as had her mother), and she recovered on penicillin treatment.—J. Lorber

Mediastinal Duplication of the Gut. J. S. Elwood*. *Arch Dis Child*, December, 1959, 34: 474–479. (*Royal Liverpool Children's Hosp., England)

Two instances of mediastinal duplications of the gut were discovered in a child of 18 months and in a day-old infant. The first was an isolated mediastinal cyst which was successfully removed at operation. The second was a jejunal duplication which passed through the diaphragm into the posterior mediastinum. It terminated in a neuromuscular strand attached to the spinal cord. This infant developed gross dyspnea and cyanosis

soon after birth and died during attempted operative removal of the cyst. Both children had associated gross vertebral anomalies. The possible modes of development of this anomaly are discussed.—J. LORBER

Fatal Miliary Coccidioidomycosis Complicating Prolonged Prednisone Therapy in a Patient with Myelofibrosis. J. CASTELLOT*, R. CREVELING, and F. PITTS. *Ann Intern Med*, January, 1960, 52: 254–258. (*Letterman Army Hosp., San Francisco, Calif.)

The first reported case of disseminated coccidioidomycosis associated with adrenocortical steroid therapy is documented in the case of a patient with a 7-year history of myelofibrosis. This report highlights the possible danger of acquisition, activation, or dissemination of coccidioidomycosis when steroid therapy is prolonged, and is considered to be the counterpart of observations recorded with reference to tuberculosis, histoplasmosis, and other infectious diseases (after authors' summary).—T. H. NOEHREN

Cryptococcosis (Torulosis). M. LITTMAN*. *Amer J Med*, June, 1959, 27: 976–998. (*Mount Sinai Hosp., New York, N.Y.)

Epidemiologic studies emphasize the wide distribution of *Cryptococcus neoformans* in nature. The disease process begins with inhalation of infected dust. There are wide variations in chest roentgenograms in pulmonary cryptococcosis, making it necessary to include the disease in the differential diagnosis of pulmonary diseases of slow evolution. The diagnosis of cryptococcosis is made by isolation of the organism and is confirmed by an identification procedure that utilizes a number of biologic and biochemical characteristics of the organism. *Cryptococcus neoformans* is classified into 3 serotypes on the basis of type-specific capsular polysaccharide, although cross reactions between these types and other microorganisms occur. Diagnostic serologic procedures, including complement-fixation tests, may provide early evidence of the disease. There is still no satisfactory antigen for eliciting skin hypersensitivity. Eleven patients with cryptococcal meningitis were treated with amphotericin B by intravenous and intrathecal routes. Seven improved considerably or returned to normal activity; 4 patients died. Of the 4 fatal cases, 3 had received only a minimal number of infusions of the agent before death. The clinical responses were excellent in 4 patients with cryptococcal meningitis who received hyperimmune gamma globulin twice weekly, intravenous and intrathecal amphotericin B, and who were maintained on low thiamin diets.—T. H. NOEHREN

Some Cases of Moniliasis in the Children's Ward of the Tuberculosis Institute at Belgrade (in Serbo-Croatian). LJ. VUCKOVIC*, M. MILOVANOVIC, A. J. -BRMBOLIC, D. ZEGARAC, and O. DJ. -JANJATOVIC. *Tuberkuloza*, No. 6, 1958, 10: 324–330. (*Tuberculosis Institute, Belgrade, Yugoslavia)

Fifteen proved cases of pulmonary tuberculosis were complicated by *Candida albicans*. Of these 15 children, 7 who were treated with nystatin responded to treatment promptly, and all of the symptoms of moniliasis disappeared after 6 days. The systemic distribution was: 3 cases in the mouth and pharynx, 2 in the gastrointestinal tract (mainly the esophagus), and 2 cases in the respiratory tract, together with bronchiectasis. Autopsy confirmed that 1 of the 15 patients died from pseudo-croup; this patient was not treated with nystatin. The other 8 patients were not treated with nystatin because they did not have all of the known symptoms of moniliasis.
—D. R. MATIASEVIC

Nocardiosis: Report of Two Cases in Children. T. F. DOLAN, JR.*, N. B. MCCULLOUGH, and L. E. GIBSON. *AMA J Dis Child*, February, 1960, 99: 234–236. (*National Institute of Allergy and Infectious Diseases, U.S.P.H.S., Bethesda, Md.)

Two cases of nocardiosis in children are reported, 1 involving the lungs, and the other, soft tissues and bone. Both cases responded to prolonged courses of treatment with sulfadiazine and penicillin, together with surgical debridement in the case involving soft tissue. The cases reported here represent 2 of the commonest clinical variations of nocardiosis, namely, pulmonary and soft-tissue disease. If therapy is to be successful, 3 major factors must be considered. First, an early diagnosis is essential, since nocardiosis usually starts as a local disease but tends to metastasize; in particular, a high incidence of brain abscess has been reported. The choice of specific therapy is important. In almost all successfully treated clinical cases, however, sulfadiazine was included in the therapy. The points of similarity of nocardiosis and tuberculosis should be kept in mind as a guide to length of treatment. The third major consideration is the employment of surgical debridement and drainage when applicable.
—M. J. SMALL

Pulmonary Nocardiosis Successfully Treated with Large Doses of Penicillin and Surgery (in Japanese). J. KAKUYA*, H. MABUNO, and T. OYA. *Jap J Chest Dis*, March, 1960, 19: 218–222. (*National Hyogo Sanatorium, Japan)

The writers report a case of pulmonary nocardiosis, an unusually rare disease in Japan, in a 23-

year-old pregnant woman. The clinical course was characterized by remittent high fever, pyothorax on the right side, and leukocytosis. The patient was treated with a total of 113.1 million units of penicillin, and her fever returned to normal levels. She underwent pleurolysis and segmental resection of the right lung with uneventful recovery. From the operative findings, it was concluded that this patient's illness originated primarily in the lung, followed by extension to the pleura and development of pyothorax and subcutaneous abscess formation under the right scapula.—I. Tateno

The Symptoms of Hypercalcemia Associated with Sarcoidosis Masquerading as Peptic Ulcer. A. Richtsmeier*. *Ann Intern Med*, June, 1959, 51: 1371–1378. (*Madison 3, Wisconsin)

Hypercalcemia with marked gastrointestinal symptomatology is described in a patient with sarcoidosis who was receiving treatment for peptic ulcer. A previously demonstrated bleeding duodenal ulcer led to the institution of ulcer therapy, followed by exaggeration of symptoms. These gastrointestinal symptoms were promptly alleviated by a reduction in dietary intake of calcium. The interrelationship of sarcoidosis, hypercalcemia, peptic ulcer, and the milk-alkali syndrome is discussed. The important signals of nausea, abdominal fullness, and vague epigastric distress should not be overlooked as presenting complaints of hypercalcemia (Author's summary).
—T. H. Noehren

Sarcoidosis With Panhypopituitarism and Diabetes Insipidus. J. Nora*, J. Levitsky, and H. Zimmerman. *Ann Intern Med*, June, 1959, 51: 1400–1409. (*Chicago Med. School, Illinois)

A patient with sarcoidosis and anterior and posterior pituitary insufficiency is described. Clinical manifestations of diabetes insipidus appeared only upon the administration of cortisone (Authors' summary).—T. H. Noehren

The Effect of a Bronchodilator Aerosol on Ventilatory Capacity in Fibrocystic Disease of the Pancreas. P. Gandevia* and C. Anderson. *Arch Dis Child*, December, 1959, 34: 511–515. (*Royal Children's Hosp., Melbourne, Australia)

Sixteen children aged 6 to 17 years who were suffering from fibrocystic disease of the pancreas (mucoviscidosis) were investigated to determine whether the use of bronchodilator drugs enhanced their ventilatory capacity. They were given an inhalation of aerosol 1:1,000 isoprenaline (isoproterenol) for 1½ to 2 minutes. Their ventilatory capacities were determined before and after the experiment, using a single-breath technique. All had some degree of infective respiratory illness which was mild in 5, moderately severe in 6, and persistently severe in 5. The response to the aerosol was consistently favorable. Those patients in the middle group showed the most improvement; in them the increase in vital capacity amounted to an average of 3.8 per cent.
—J. Lorber

Chronic Pneumonitis of the Cholesterol Type (in Italian). G. Maggi*, E. Pansa, and F. Rolfo. *Minerva Med*, No. 92, 1959, 50: 3691–3698. (*Ist. Pat. Chirurgica, U. of Turin, Italy)

This paper contains the clinical and therapeutic observations and pathogenic interpretation of 17 cases of chronic pneumonitis of the cholesterol type. The clinical and anatomic patterns of the disease are given with its main characteristics of: prevalence in the masculine sex (11 cases out of 17), occurrence in the fifth or sixth decades of life, localization in the upper lobes of the lung (12 cases), and chronicity. The diagnosis, sometimes particularly difficult to distinguish from cancer of the lung, should be based upon the following elements: (*1*) exceptionally long duration of symptomatology, with relapses of bronchopneumonitis; (*2*) heavy and continuous thoracic pain in a high percentage of cases; (*3*) presence of a roentgenographic shadow, mostly in the upper lobes; (*4*) presence of several cavities in this opacity, and pleural thickening; (*5*) slight alteration of the bronchographic aspect of the more peripheral branches of the bronchial tree. When diagnosis is still doubtful, biopsy can be of great help. Basing the interpretation upon experimental data obtained in rabbits, in which an inflammatory process of the lung was caused by different agents, and a high cholesteremia was produced by the endovenous injection of Triton® WR-1339, it is concluded that the disease can probably follow bronchopneumonitis due to varied etiology, that the process is possible because of an inflammatory reaction of the small bronchi, and that the accumulation of cholesterol is a consequent process.—I. Archetti

"Occult" Carcinoma of the Bronchus: A Study of 15 Cases of *in Situ* or Early Invasive Bronchogenic Carcinoma. Z. Woolner*, H. Andersen, and P. Bernatz. *Dis Chest*, March, 1960, 37: 278–288. (*Mayo Clinic, Rochester, Minnesota)

A survey was made of those cases of resected bronchogenic carcinoma in which the lesion was occult in that no tumor was visible on gross examination of the specimen. The duration of symptoms, when present, ranged from 3 weeks to

7 months: cough, slight hemoptysis or, more frequently, an episode of pneumonitis were responsible for further investigation. In 11 cases evidence of pneumonitis as seen by roentgenography was substantiated. In all of the cases, the shadow observed on the roentgenogram was apparently the result of varying degrees of associated peripheral pneumonitis rather than a tumor in the lung. Cytologic examination of either sputum or bronchial secretions gave positive results in 73 per cent of the cases. Results of bronchial biopsy were positive in 47 per cent. Follow-up data indicate that the lesion is curable at this stage of evolution, but the danger of recurrence of carcinoma *in situ* in the stump is pointed out by the occurrence of this complication in 1 case 3 years after operation.—E. A. Rouff

Extrapulmonary Manifestations of Bronchogenic Carcinoma. J. H. Knowles* and L. H. Smith, Jr. *New Engl J Med*, March 10, 1960, 262: 505-510. (*Harvard Med. School, Boston, Mass.)

This paper reviews the literature on the large number of extrapulmonary manifestations that have been described in association with carcinoma of the lung. These syndromes are outlined as follows: Metabolic abnormalities: Cushing's syndrome; hypercalcemia; excessive antidiuretic hormone; and carcinoid syndrome. Neuromuscular abnormalities: cortical cerebellar degeneration; peripheral neuropathy (sensory or sensorimotor); dementia and psychosis; mixed forms; and carcinomatous myopathy or polymyositis. Connective-tissue and osseous abnormalities: clubbing and generalized hypertrophic osteoarthropathy; dermatomyositis; scleroderma; and acanthosis nigricans. Vascular (endothelial) abnormalities: migratory thrombophlebitis; and nonbacterial thrombotic endocarditis. Hematologic abnormalities: anemia—hemopathic hemolytic and symptomatic hemolytic; fibrinolytic purpura; and cryofibrinogenemia.

None of these disorders are pathognomonic of bronchogenic carcinoma, all being occasionally found in association with other malignant tumors. Few of these associated syndromes can be adequately explained on the basis of current concepts of the metabolism of neoplastic tissue, nor can they be related to any known function of normal respiratory epithelial cells. One or more of the associated syndromes may initiate the symptomatology of a primary lung tumor. In this context, awareness of the possible significance of the syndrome may lead to earlier diagnosis and treatment of cancer than would otherwise be possible. —M. J. Small

Primary Fibrosarcoma of the Bronchus. P. Holinger*, K. Johnston, N. Gosswеiler, and E. Hirsch. *Dis Chest*, February, 1960, 37: 137-143. (*U. of Illinois School of Med., Chicago)

A case of primary fibrosarcoma in a 5½-year-old boy is presented as being the ninth authenticated case reported in the literature. The diagnosis was established by bronchoscopic biopsy and the tumor was successfully removed by a right middle and lower lobectomy. The symptoms presented are usually typical of persistent bronchial obstruction. Even though endobronchial removal of the tumor may seem feasible, it is not believed that this is adequate therapy. Because of the high recurrence rate (60 per cent), lobectomy is the procedure of choice.—E. A. Rouff

Case Reports. Eosinophilic Granuloma of the Rib. G. C. Godfrey*, J. M. Miller, and M. Ginsburg. *US Armed Forces Med J*, February, 1960, 11: 217-223. (*V. A. Hosp., Ft. Howard, Md.)

Although the cause is unknown, eosinophilic granuloma appears to be closely associated with the Letterer-Sieve and Hand-Schüller-Christian diseases. If the three diseases are but different stages of one pathologic condition, eosinophilic granuloma is the benign form which occurs in young adults and may affect bone and lung as well as other sites. The case histories of eosinophilic granuloma of the rib in 2 men 27 and 31 years old are presented together with a general discussion of the differential diagnosis and methods of treatment.—C. H. Pierce

TUBERCULOSIS, PULMONARY

The Psychiatric Approach to Tuberculosis. B. C. Archer*. *S Afr Med J*, March, 1960, 34: 242-244. (*Durban, Union of South Africa)

The common emotional reaction to tuberculosis is mild anxiety or depression or, defensively, an attitude of defiance and ultra-cheerfulness. Apathy is rare except early or late in the disease. The physician's attitude when diagnosing or hospitalizing is important in easing the in-hospital adjustment. Group therapy may be of value in the patient's adjustment. Short hospitalization has increased the need for team-approached rehabilitation (doctor, relatives, social worker, et cetera). In the African, the insidious onset of disease is less common than the acute and fulminating. To overcome the tendency of the African to leave the hospital as soon as he feels better, hospital design and attitudes should attempt to give him a sense of community. Mothers are more content when their newborn babies are left with them. When given prophylactic isoniazid, tuber-

culosis is prevented in these infants. They do not develop immunity, and when the drug is stopped they may become infected if they are exposed. —E. J. Cassell

Two Cases of Cavitary Lung Disease with Photochromogenic Mycobacteria (in German). L. Reinhold*, W. Kölzsch, B. W. Schmidt, and R. Walter. *Z Tuberk*, December, 1959, 114: 163–171. (*Institut für Medizinische Mikrobiologie, Halle (Saale), Germany)

Two cases are reported of cavitary disease in the lungs which evidently was caused by photochromogenic mycobacteria. A special feature in 1 case was the discovery of the same bacteria in the fluid, which was aspirated from the knee joint. Gonitis had appeared while the patient was under treatment for the lung disease. —J. Haapanen

The Effects of Gastrectomy on the Course of Tuberculosis of the Lungs (in German). H. Neubert*. *Tuberkulosearzt*, January, 1960, 14: 22–28. (*Heilstätte Strüth über Ansbach, Mittelfranken, Germany)

The case records of 2,515 men with pulmonary tuberculosis were examined. It was found that 202 (8 per cent) had undergone gastrectomy, that 16 of these patients had tuberculosis before the operation, and that in 14 of the latter group a progression of the tuberculous process had occurred 2 months to 8 years after the operation. From an analysis of the data, the following conclusions are drawn: (*1*) Gastrectomy promotes the development and progression of a tuberculous infection of the lungs. (*2*) Tuberculous patients who have undergone gastrectomy are markedly less responsive to therapeutic measures and, therefore, require more extensive treatment and longer hospitalization than do other patients. (*3*) The incidence of relapses is also higher in these cases.—J. Haapanen

Pulmonary Tuberculosis Associated with Kartagener's Syndrome (in German). H. Eule*. *Z Tuberk*, December, 1959, 114: 189–194. (*"Waldhaus," Sommerfeld, Kreis Oranienburg, Germany)

A report is given of 2 cases of Kartagener's syndrome with pulmonary tuberculosis. As a special feature, 1 of these patients was treated with collapse procedures and, finally, the cavities closed and the sputum became negative for tubercle bacilli. The bronchiectatic changes remained the same after this treatment.
—J. Haapanen

The Middlebrook-Dubos Test and the Erythrocyte Sedimentation Rate in the Evaluation of the Degree of Activity of Tuberculosis (in Italian). G. Brenna* and N. Di Mauro. *Minerva Med*, No. 75, 1959, 50: 2949–2956. (*Osp. Trabattoni, Seregno, Italy)

The Middlebrook-Dubos test and the erythrocyte sedimentation rate were used to evaluate the degree of activity of tuberculosis in 5 groups of patients in different stages of the disease. A group of 129 normal persons served as controls. It was found that both tests showed high values in patients with evolutive forms, rather lower values in those with well circumscribed and stationary forms, and still lower values in those recovering from the disease. According to these data, it is thought that the results obtained in patients with stationary forms were of particular value and interest, because they should be characteristic of the special immune equilibrium found in those patients. For that reason the use of both tests could be of some help in evaluating the condition of the patient and the possibility of either surgical or other therapeutic treatment.—I. Archetti

Paralysis of the Diaphragm in Patients with Pulmonary Tuberculosis (in Serbo-Croatian). Lj. Volceva* and R. Mihailovska. *Tuberkuloza*, No. 5, 1958, 10: 293–295. (*Children's Hosp. "Zdravlje," Skoplje, Yugoslavia)

Three cases are described of primary pulmonary tuberculosis associated with paralysis of the diaphragm due to paralysis of the left phrenic nerve. It is believed that unilateral paralysis of the diaphragm is caused by tuberculous infection which affects the phrenic nerve early and irreversibly. The persistence of paralysis after healing of the tuberculous process in the lung is the main basis for this theory.—D. R. Matiasevic

TUBERCULOSIS, NONPULMONARY

Puerperal Erythema Nodosum after Liver Extract Injections. Treatment with Prednisone. F. D. C. Ford*. *Brit Med J*, February 6, 1960, No. 5170: 400–401. (*Guildford, Surrey, England)

Two cases of erythema nodosum are reported. Both occurred in multigravidae within a month of confinement, in 1 case 30 days and in the other 19 days after intramuscular injections of Anahaemin (Bardin). It is suggested that the erythema nodosum was an allergic reaction induced by this substance. In the second case, prednisone appeared to hasten recovery (after author's summary).—E. A. Riley

Experiences in the Treatment of Tuberculous Meningitis in Children (in German). O. LOMBOS* and L. SZÖNYI. *Z Tuberk*, December, 1959, 114: 158–163. (*Kinderklinik, Pécs, Hungary)

Since January, 1949, 133 cases of tuberculous meningitis have been treated in the pediatric hospital at Pécs. These were divided into 4 groups according to the type of treatment. In the first group a good therapeutic result was obtained in only 43 per cent of the cases with intramuscular and intrathecal streptomycin, whereas in the fourth group, which was treated with the following method, the percentage was 94. This treatment consisted of 15 to 20 mg. of isoniazid per kg. of body weight daily for at least 8 months, and 20 to 25 mg. per kg. of streptomycin intramuscularly twice daily for 3 months. Only 3 relapses were recorded, evidently due to medical treatment of insufficient length. Froin's syndrome was observed in 8 cases; 5 of these were cured by isoniazid treatment.—J. HAAPANEN

The Morbidity from Pulmonary Tuberculosis in Patients Suffering from Extrapulmonary Tuberculous Disease, Lupus Vulgaris Cutis. K. CLASEN and O. HORWITZ*. *Adv Tuberc Res*, 1960, 10: 237–255. (*Finsen Institute, Copenhagen, Denmark)

The morbidity from pulmonary tuberculosis was examined among 3,902 patients with lupus vulgaris cutis admitted to the Finsen Institute during the years 1895–1954. The observation period, an average of 24 years, was calculated from the time of admission to the Finsen Institute until the diagnosis of pulmonary tuberculosis, viz., the death of the patient, or the termination of the present investigation on December 31, 1954. A total of 547 cases of pulmonary tuberculosis were demonstrated among the lupus patients, corresponding to a mean rate of 6,000 per 1 million person-years. This rate must be considered as a minimum, as many of the patients did not have a roentgenogram taken. This was confirmed by the rate being twice as great in a group of patients who all had a roentgenogram taken; 255 of the 547 cases of pulmonary tuberculosis were found on admission, giving a rate of 65,000 per 1 million, while 292 cases were found during the follow-up period, corresponding to a rate of 3,000 per 1 million person-years. Among 462 lupus patients, representing 91 per cent of the patients admitted during the period 1935–54, 250 showed pathologic changes in the first roentgenogram taken. In 64 of them the lesions were evaluated as active tuberculosis (14 per cent), in 87 as inactive tuberculosis (19 per cent), in 86 as mere calcifications (19 per cent), and in 13 as findings of unknown etiology (3 per cent). The percentage of lesions increased with age. The morbidity from pulmonary tuberculosis among patients with lupus was found to be 4–10 times greater than in the general population. It is, therefore, important that persons who have, or have had, lupus should be included in tuberculosis case-finding programs. The majority of the cases of pulmonary tuberculosis found may be regarded as postprimary phthisis (after authors' summary).

UPPER RESPIRATORY TRACT DISEASE, BACTERIAL

Studies of Pathogenic Staphylococci Among the Staff in a Department of Medicine and Infectious Diseases. T. HOFSTAD* and T. M. VOGELSANG. *Acta Path Microbiol Scand*, Fasc. 2, 1960, 48: 140–168. (*U. of Bergen School of Med., Norway)

Pp. 140–148: A long-term study has been made of the carrier rate of pathogenic staphylococci in the noses and throats of members of the staff in a department of medicine and infectious diseases. Repeated swabs were taken from the nasal cavities and from the throat at weekly intervals for 3½ months. Five to 15 swabbings were taken from 100 members, 1,146 times in all. Thirty-five per cent of the nose swabs and 48 per cent of the throat swabs yielded pathogenic staphylococci. Of those studied, 34 were permanent and 54 intermittent staphylococcal carriers. Ten permanent and 12 intermittent carriers would have been missed if the throats had not been swabbed also. On an average, the nasal swabbings showed a heavier growth of pathogenic staphylococci than did the throat swabbings. This was most marked among the permanent carriers. There was a fairly constant rate of carriage during the whole examination period.

Pp. 149–154: Of the 980 pathogenic strains isolated, only 10 per cent were resistant to penicillin, and 9 per cent to streptomycin. Only a few strains were resistant to the other antimicrobials used. Compared with earlier examinations, this decrease in drug-resistant strains is remarkable. A somewhat higher number of resistant strains was found in the nasal cavities than in the throat and, furthermore, among the intermittent carriers rather than the permanent carriers. The reason for the decline in drug resistance is to be found not only in a greater reservation in the use of these antimicrobials and in individual calculation of the dosage but, also, in a tightening up of the hygienic precautions in the department.

Pp. 155–163: The staphylococcal strains isolated from the upper respiratory tracts of 100 members

of the staff were examined for the frequency of lysis by 21 different phage filtrates consisting of the basic phage set. Only 48 per cent of the 980 strains isolated were typable by the Routine Test Dilution (RTD), while as many as 39 per cent were lysed by employing phages at 1,000 times the concentration used in the RTD, giving a result of 87 per cent typable strains. Phage group III was the predominant group, both in the whole series and among the antimicrobial-resistant strains, amounting to 36 and 51 per cent of the typable strains, respectively, followed by group I with 26 and 31 per cent. Of the 222 typable strains belonging to group I, 60 were lysed by phage 80 only. One-fourth of these strains were resistant to penicillin and streptomycin and resistant or slightly susceptible to tetracycline. Otherwise, the great majority of strains resistant to 3 or 4 drugs was confined to group III. The permanent carriers had a tendency to retain strains of the same antimicrobial susceptibility and phage pattern, which impeded the implantation of other strains. Of the 34 permanent carriers, only 8 showed constant colonization with drug-resistant strains, while 35 of the 54 intermittent carriers gave periodic growth of such strains (after authors' summary).

Pp. 164–168: Members of the staff who had previously taken part in a long-term study of the carrier state were examined before leaving for 3 to 4 weeks' holiday, and upon their return to the hospital. The permanent carriers for the most part retained their staphylococcal strains for a very long time, and this had a tendency to impede the implantation of other strains on the mucosa. In a department contaminated with staphylococci which cause infections, they have not the same possibilities of picking up the endemic strain as do the intermittent carriers. Intermittent carriers who harbor the endemic strain in their upper respiratory tracts may get rid of this strain by moving from the contaminated clinical ward. However, in 8 of the 22 cases of intermittent carriage, an absence of 3 to 4 weeks was not sufficient for this purpose.—E. DUNNER

UPPER RESPIRATORY TRACT DISEASE, VIRAL

Antibody Crossabsorptions between Influenza A_2-Strains. A. HARBOE* and R. REENAAS. *Acta Path Microbiol Scand*, Fasc. 2, 1960, 48: 133–139.

Antibody crossabsorption between the A/Japan/305/57 and A/Singapore/1/57 strains did not reveal any qualitative, antigenic difference between these strains. When sera against 3 Norwegian A_2-strains were intensively absorbed with A/Singapore/1/57, some antibody to the 3 strains and to A/Japan/305/57 still remained. Strains isolated from 2 epidemic waves of Asian influenza in a small community were compared with each other in cross-absorption tests and showed no difference.—E. DUNNER

Influenza A_2-Strains Against A and A_1-Strains in Cross-Haemagglutination Inhibition Tests. A. HARBOE*, R. REENAAS, and K. JUUL. *Acta Path Microbiol Scand*, Fasc. 3, 1960, 48: 231–242. (*State Institute for Public Health, Oslo, Norway)

The experiments failed to provide conclusive evidence of the existence of antigenic factors common to A_2 (Asian) and any other influenza A strains.—E. DUNNER

THORACIC SURGERY

Therapy of Postoperative Empyema after Pneumonectomy and Partial Lung Resections (in Russian). I. S. KOLESNIKOFF* and S. N. SOKOLOFF. *Groud Khirurgiia*, January—February, 1960, 1: 67–73. (*Surgical Hosp. of Med. Military Academy, Kiroff, U.S.S.R.)

Previous treatment of postoperative empyema by closed catheter drainage and intrapleural instillation of antimicrobials resulted in early improvement but eventually poor results from pleural sclerosis, prolonged course, and debilitation. In contrast, 166 patients aged 16–64 are reported, 28 following malignancy, 62 tuberculous, and 76 suppurative. In 82, pneumonectomy had been done; in 84, lesser resection. These patients were treated by aspiration (daily at first) and instillation of appropriate antimicrobials. Recovery from empyema after pneumonectomy averaged 45 days; after lesser resection, 10 days. In cases of tuberculosis and bronchopleural fistula, early thoracoplasty was performed. In cases with pleural pus pockets and old empyema, thoracotomy and clearing out were done, followed by aspirations. Pleurocutaneous fistulas were excised and sutured successfully in 3 instances; good results followed uniformly, although pleural space obliteration was incomplete in post-malignancy cases. In some cases both methods should be combined. In the period 1953–1956, good results were achieved with aspirations in 50 per cent; mortality occurred in 3.5 per cent. In 1957, good results were obtained in 75 per cent, and mortality decreased to 0.9 per cent. In 1958, all cases had good results, and the mortality was zero.—M. KOMARJANSKI

Some Observations on Broncho-Pleural Fistula Following Lung Resection. S. Anand*, W. Singh, and I. Pathak. *Indian J Chest Dis*, January, 1960, 2: 19–23. (*Medical College, Amritsar, India)

The development of bronchopleural fistula is a very serious complication, especially in cases of tuberculosis of the lung, and increases the morbidity of pulmonary resection. The reported incidence of this complication, throughout the world, varies from 5 to 15 per cent. In the present series (138 cases) it developed in 20 cases, an incidence of 14.4 per cent. Early diagnosis and conservative therapy were shown to give better results, with stabilization or curing of 65 per cent of the cases. Drainage should be established as soon as the diagnosis is made, and thoracoplasty should then be carried out as soon as the patient can tolerate the operation.—E. A. Rouff

Experiences in the Surgical Treatment of Pulmonary Paragonimiasis—Removal of the Worm without Resection of the Lung (in Japanese). K. Shibuya*, E. Kashima, S. Araki, and H. Nagao. *Clin Resp Org*, March, 1960, 15: 220–224. (*Toyooka Municipal Hosp., Hyogo Prefecture, Japan)

The writers operated on 10 patients with pulmonary paragonimiasis; in 6 cases, removal of the worm only—without lobectomy—brought about uneventful recovery. The following statements are made: (*1*) When a cystic shadow is demonstrated by roentgenography, the worm (*Paragonimus westermani*) may be absent and the cyst may be histologically cured in some cases. (*2*) A fresh cyst which cannot be demonstrated by roentgenography may be present. (*3*) When the worm is removed, the cyst undergoes a rapid repairing process. (*4*) Pleural involvement is quite severe, and lobectomy may result in impaired pulmonary function. Pleurisy was the initial stage of the illness in 3 of the 10 cases. (*5*) Surgery restricted to removal of the worm is a safe procedure and may be performed on patients who have multiple lesions in both lungs.—I. Tateno

Treatment of Extensive Cavitary Tuberculosis. II. Endocavitary Aspiration (in Serbo-Croatian). T. Furlan* and N. Fink. *Tuberkuloza*, No. 5, 1958, 10: 255–260. (*Tuberculosis Hosp., Golnik, Yugoslavia)

From 1945 to 1958, 89 endocavitary aspirations were performed. It is concluded that cavity drainage should always be attempted when it might eliminate the necessity of pneumonectomy. Of the 89 patients under review, 20 had drainage in combination with thoracoplasty. In 45 per cent, recovery was permanent; 22 per cent of the drained cavities were situated in the sixth segment. The therapeutic indications are discussed, and endocavitary aspiration is suggested particularly for bullous cavities with fluid levels, no matter where they may be situated. This is of value for giant cavities in the lower region with simultaneous insignificant lesions in the apex. Endocavitary aspiration is the method of choice in giant cavities of the apical region. It is recommended that endocavitary aspiration should be given widespread application in countries where such forms of pulmonary tuberculosis exist, as is the case in Yugoslavia.—D. R. Matiasevic

Pneumonectomy for Tuberculosis: An Evaluation of 124 Cases. J. E. Hiltz*, V. D. Schaffner, and G. A. Kloss. *Canad Med Ass J*, February 27, 1960, 88: 457–471. (*Nova Scotia Sanatorium, Kentville, N. S.)

A review is made of 124 pneumonectomies for tuberculosis performed between 1945 and 1959. The operations were done on the right side in 51 and on the left in 73. Ninety-five patients (76 per cent) had far advanced disease (47 patients—38 per cent—had no disease in the contralateral lung); 54 (43 per cent) had minimal disease; and 23 (19 per cent) had moderately advanced disease. Fifty-seven patients (46 per cent) developed a total of 135 complications which included spread, bronchopleural fistula, stubborn space, empyema, ulceration of stump, and early death. The highest incidence of complications was in the 50–59-year age group. Thirty (59 per cent) of the patients with right-side pneumonectomies developed complications, compared with 27 (37 per cent) of those with left-side pneumonectomies. The majority of resections was done for extensive residual disease with or without bronchiectasis and residual cavity. The highest incidence of complications developed in patients with persisting cavities and positive sputum. The presence of previously existing tuberculous bronchitis did not greatly influence the development of complications.

Among 108 patients with a follow-up of 2 years or longer, 51 were greatly improved. Twenty-four of these had negative sputum. Of the 84 who had their operations 5 or more years ago, 52 (62 per cent) were so classified. Of the 35 persons in the 10-year group, only 6 are known to be alive, 21 having died of tuberculosis and 8 of nontuberculous causes. In this series there were 11 deaths within 60 days of operation, a mortality rate of 9 per cent. No death has occurred after the sixth postoperative year. The first-year mortality between 1945 and 1949 was 30 per cent, as compared with 11 per cent for subsequent years. The over-all death rate from both tuberculous and nontuberculous causes was 23 per cent.—E. A. Riley

Resection for Pulmonary Tuberculosis in Infants and Children. J. Igini*, R. Fox, and W. Lees. *Dis Chest*, February, 1960, 37: 176–184. (*Municipal Tuberculosis Sanatorium, Chicago, Illinois)

The indications for pulmonary resection in children are essentially similar to those in adults. It has clearly been shown that resection is a safe and effective mode of therapy for selected children. In the present series, of 35 children ranging in age from 2 years and 9 months to 15 years, the mortality rate was 2.9 per cent. All of the surviving patients are living and well with no sign of active pulmonary disease within a 48-month follow-up period.—E. A. Rouff

The Residual Lesion in Pulmonary Tuberculosis Requiring Surgery: A Review of 100 Sputum-Negative Patients Consecutively Operated on. I. Kass*, T. Miyamoto, J. Denst, G. J. Wittenstein, W. F. Russell, Jr., G. Middlebrook, and S. H. Dressler. *New Engl J Med*, February 18, 1960, 262: 315–320. (*National Jewish Hosp., Denver, Colorado)

To answer the question whether the residual lesion requires surgery, 100 patients with pulmonary tuberculosis, whose sputum was negative for tubercle bacilli, consecutively operated on between January, 1956, and January, 1958, were evaluated and the data analyzed in this report. Seventy-nine of the 100 patients with negative sputum were shown to have acid-fast bacilli in the resected specimens by some combination of direct smear, culture, or histologic study; 80 per cent of the closed necrotic lesions, as opposed to 63 per cent of open cavities, contained acid-fast bacilli. The nodular lesion and the inspissated cavity in patients with persistently negative sputum appear, from the presence of stainable acid-fast bacilli, to be less amenable to the effects of chemotherapy than is the open cavity. Although the risk attending resection in sputum-negative patients was negligible, at present surgery is recommended for round lesions of undetermined etiology, symptomatic tuberculous bronchiectatic lesions, patients excreting drug-resistant organisms before conversion, patients in whom sudden bacteriologic remission was not attributable to chemotherapy, patients with ethnic predisposition to progressive tuberculosis, and those in whom sociologic factors would preclude adequate therapy or follow-up study.

The patient who has negative sputum at the time of admission, and the patient excreting organisms susceptible to both streptomycin and isoniazid who has responded or is responding with bacteriologic conversion of sputum (not attributable to blockade of the bronchocavitary junction), and who can be expected to adhere to a regimen of adequate and sustained medical therapy and follow-up study, need not undergo surgery for the following types of residual lesions: bilateral lesions; the open-negative syndrome; nodular disease and inspissated cavities; and residual infiltrations, regardless of anatomic extent.
—M. J. Small

Results of Surgical Treatment of Pulmonary Tuberculosis with Special Regard to Resection Therapy (in Serbo-Croatian). S. Goldman*, B. Lavric, T. Furlan, I. Papo, J. Studic, and I. Cestnik. *Tuberkuloza*, No. 2, 1959, 11: 147–165. (*Presented at the 11th Congress of Phthisiologists of Yugoslavia)

A report is given of 680 resections performed up to 1957, and of 285 thoracoplasties and 642 extrapleural pneumolyses performed up to 1959. The 680 resections comprised: 137 partial lobectomies, 293 lobectomies, 158 pneumonectomies, and 92 combined operations. The results obtained in these 680 cases, which were divided into "ideal," "average," and "bad" indication groups, are described. It is concluded that really successful resection therapy can be expected only when the indications are close to ideal, thus excluding cavitary cases. In worse cases, preference should be given to surgical collapse, if only as a palliative measure, as the risk is less and the results not too poor, according to the authors.
—D. R. Matiasevic

Excavated Haematomas after Pulmonary Segmental Resection. H. Beumer* and T. Mellema. *Dis Chest*, February, 1960, 37: 163–167. (*Sanatorium Berg en Bosch, Bilthoven, The Netherlands)

Following a change in surgical technique, 16 excavated hematomas developed in the intersegmental plane from a total of 342 segmental resections. Generally, the hematoma disappeared spontaneously, without any symptoms or complications. The cause is considered to be the strong negative suction in the drainage catheters—between 40 and 100 cm. of water—in use during the postoperative period.—E. A. Rouff

Myelolipoma of the Mediastinum. H. Litwer*. *Radiology*, March, 1960, 74: 471–473. (*V.A. Center, Martinsburg, W. Va.)

Myelolipomas are uncommon tumorlike masses composed of heterotopic bone marrow and adipose tissue. They usually occur in the adrenal glands, but have been reported in other parts of the body, occasionally in the chest. Although they may be without demonstrable relation to other disease, they are sometimes found in association with severe anemias. Two cases of myelolipoma of the

mediastinum are reported, both associated with congenital hemolytic anemia (hereditary spherocytosis) and demonstrable on the chest film. The tumors evidently had produced no deleterious effects. In 1 case the myelolipoma had been present for at least 25 years without significant change. —W. J. STEININGER

ROENTGENOGRAPHY

Arteriovenous Aneurysms, Fistulas, and Anastomoses of the Lung (in Italian). G. LUZZATTI*. *Minerva Med*, No. 69, 1959, 50: 2629–2645. (*Osp. Maggiore, Milan, Italy)

Four cases of pathologic pulmonary arteriovenous communications are described. One was a case of diffuse pulmonary angiomatosis in a 22-year-old patient (a case of pulmonary localization of Rendu-Osler-Weber's disease); 1 was a vascular malformation in a 4-year-old child; the third was an arteriovenous fistula in a large vessel of a 33-year-old woman; and the fourth was that of a communication between the very small arteries and veins, with the exclusion of the capillary bed, in a 28-year-old woman. The first 2 diagnoses were substantiated by surgery. For the latter 2 cases, the hypothesis is considered that they could have been the result of an anomalous dilatation of the precapillary anastomoses in the normal lung, as described by von Hayek. —I. ARCHETTI

Chronic Bronchitis and Emphysema at Bronchography. Survey of Diagnostic Features Obtained by Reviewing 2,000 Bronchograms. A. K. FREIMANIS and W. MOLNAR*. *Radiology*, February, 1960, 74: 194–205. (*Ohio State U. Health Center, Columbus)

Chronic bronchitis and emphysema result in a wide range of bronchographic abnormalities. In a study of 2,000 bronchograms, chronic bronchitis was observed to produce spasm, increased and abnormal secretions, bronchial obstruction, irregularity and deformity of the bronchial wall, patchy alveolarization, mucous gland dilatation, atrophy of the bronchial mucosa, incomplete or irregular peripheral filling, abnormalities in the smaller bronchial branches ("pools," "spiders," and "bronchiolectases"), and inflammatory diverticula. The multiple pathologic changes in this entity and their importance in the understanding of chronic bronchitis and emphysema are emphasized. Bronchography yields valuable information about an extensive part of the bronchial tree not accessible to other examinations.—W. J. STEININGER

Localized Emphysema. S. BRUNNER* and O. POCK-STEEN. *Acta Radiol (Stockh)*, March, 1960, 53: 184–190. (*Rigshospitalet, Copenhagen, Denmark)

The condition of localized emphysema, described as increased air content in the pulmonary tissue, has received little attention in comparison with solitary or multiple air-filled cavities of the lungs generally referred to as "cysts." Miller (1929) first described bullae and blebs. It is considered reasonable to think of blebs, bullae, and localized emphysema as one clinical entity.

The pathogenesis of this entity is discussed. Localized emphysema is accepted as a sign of partial bronchial obstruction from such causes as mucosal hypertrophy, deficiency or absence of cartilaginous bronchial rings, tumors, and vascular rings. The common signs are dyspnea, usually on exertion; and the less common are cough, expectoration, and chest pain. The signs and symptoms are not apt to be typical, as they may accompany other lung diseases. Roentgenographically the condition is seen as an area more translucent than the remainder of the lung. Lung cysts, by contrast, are always surrounded by a fairly distinct wall. Isolated blebs are more difficult to diagnose; however, multiple blebs generally form a honeycomb-like area. Fourteen cases are presented in an effort to explain the origin of localized emphysema. A reasonable explanation was found in only 4 cases. In the others, the mechanism remained obscure. —E. SHABART

Roentgenographic Aspects of Certain Bones in Emphysematous Patients with Chronic Bronchitis and Polycythemia (in Italian). P. TRIVELLA* and S. CHELLA. *Minerva Med*, No. 89, 1959, 50: 3565–3567. (*Ist. Semeiotica Med., U. of Pisa, Italy)

A group of 12 emphysematous patients aged 38 to 55, with chronic bronchitis and polycythemia, was studied with special emphasis on the roentgenographic aspects of certain bones (the skull, pelvis, humerus, radius, ulna, femur, tibia, and fibula). Small bone alterations of the porotic type were almost constantly observed, especially in the skull; sclerotic changes were found only in the long bones of 2 patients. In spite of their slight degree, these processes have to be considered abnormal, not connected with the age of the patients, but due to the disease: they could be caused by the venous stasis determined by the chronic condition of cor pulmonale—which acts mechanically by increasing the pressure in the bones—and by the evident hypoxia, which causes trophic disturbances.—I. ARCHETTI

Permanent Endobronchopulmonary Medication (in Italian). L. Bonelli*, L. Baglione, D. Rochat, and G. Bologna. *Minerva Med*, No. 83, 1959, 50: 3275–3290. (*Osp. S. Luigi Gonzaga, Turin, Italy)

Polyethylene tubes, 1.8 to 2.4 mm. in diameter, were introduced into the bronchial trees of 97 patients (8 with bronchiectasis, 4 with pulmonary abscesses, and 85 with cavitary tuberculosis) through the membrane between the cricoid and thyroid cartilages, in order to affort permanent medication of the bronchial and pulmonary pathologic foci. In 1 case the tube was left in for a period of 6 months; the tube should be changed every 10 days to ensure that it is still intact. The technique of the entire operation is given in detail. No serious complications were encountered with this method (only 2 cases of light subcutaneous emphysema and 4 cases in which the tube broke). The results obtained were favorable in 52 patients, unchanged in 28, and worsened in 5. Given the simplicity of the technique and the results reached in applying it, it is thought that this method should be introduced into local pulmonary therapeutics.—I. Archetti

Bronchographic Findings in Retracting Fibrothorax (in Italian). V. Donadio* and E. Galli. *Minerva Med*, No. 88, 1959, 50: 3524–3531. (*Cl. Medica, U. of Turin, Italy)

It is often difficult to visualize the alterations of the pulmonary parenchyma and bronchial branches when there is a chronic retracting fibrothorax. In these cases, bronchography can be of some help, particularly when clear definition of the entity and of the localization of the bronchial alterations due to the cavitary chronic processes are necessary for a better understanding of the clinical pattern and a consequent effective therapy. Some of the indications for bronchography are given, with accompanying examples chosen from clinical cases, but it is emphasized that these criteria are not the only ones, and they can change according to the individual case. —I. Archetti

Intralobular Sequestration with Anomalous Artery (in Japanese). S. Kishimoto*, Y. Sato, and T. Kiyama. *Jap J Thor Surg*, February, 1960, 13: 153–157. (*Hanta Hosp., Okayama City, Japan)

The writers report a case of intralobular sequestration of the lung seen in a 24-year-old male patient whose chief complaints were cough and sputum of 1½ years' duration. An abnormal shadow was found in the left lower lobe into which radiopaque material did not enter by bronchography. Thoracotomy revealed a fist-sized soft mass with an abnormal artery 7 mm. in diameter originating from the descending aorta. A resected specimen revealed a multilocular cyst in the posterior and lateral basal segments of the left lower lobe. The histologic findings were characteristic of intralobular sequestration. A brief review of the Japanese literature is given; this case was the seventh of this condition so far reported in Japan.—I. Tateno

The Atelectatic Complex of the Left Lung. B. Nordenstrom* and J. Novek. *Acta Radiol (Stockh)*, March, 1960, 53: 177–183. (*Karolinska Sjukhuset, Stockholm, Sweden)

The theories on the mechanisms of development in lamellary atelectasis are briefly discussed. Lamellary atelectasis usually affects the lingula of the left lung, and is usually associated with left lower lobe atelectasis. This atelectasis of the left lower lobe causes displacement of the lower mediastinum to the left. The upper lobe develops compensatory emphysema and rotates downward and anteriorly, thereby causing kinking of the bronchi and parenchyma of the lower lingula against the diaphragm. This kinking leads to lamellary atelectasis. The importance is pointed out of recognizing this secondary lamellary atelectasis of the lingula as masking a more important massive atelectasis of the lower lobe. The condition is more commonly seen on the left side, probably because the lingular bronchi are steeper toward the diaphragm than are the bronchi of the middle lobe.—E. Shabart

Radiation Reaction in the Lung: Report of a Fatal Case in a Patient with Carcinoma of the Lung, with Studies of Pulmonary Function before and during Prednisone Therapy. T. Rodman*, S. Karr, and H. Close. *New Engl J Med*, March 3, 1960, 262: 431–434. (*V.A. Hosp., Philadelphia, Penn.)

A case is reported in which a severe radiation reaction in the lungs followed rotational technique X-ray treatment for an anaplastic bronchogenic carcinoma located in the upper mediastinum. Pulmonary function studies were done before and repeated during a course of adrenocorticosteroid therapy, which produced remarkable amelioration of respiratory symptoms. The pulmonary function studies showed the pattern of restrictive lung disease, with an "alveolarcapillary block" that became slightly worse while the patient was receiving prednisone. Rotational X-ray therapy should be used only when the lesion to be irradiated can be encompassed with a narrow portal. Adrenocorticosteroids do not alter the progress of a radiation reaction, although subjective symptoms may be ameliorated (after authors' summary).—M. J. Small

Arterial Malformation in the Superior Mediastinum. S. Brunner*, P. Gammelgard, O. Petersen, and O. Storm. *Acta Radiol (Stockh)*, February, 1960, 53: 105–112. (*University Hosp., Copenhagen, Denmark)

Anomalies of the great vessels in the superior mediastinum are well detailed by venous and selective angiocardiography as well as thoracic aortography. Endoscopy seldom reveals the nature of these conditions. By pressure on the trachea and/or the esophagus, these vessels give rise to stridor and/or dysphagia. The most important vascular anomalies according to Gross are illustrated and discussed. Roentgen examination of the esophagus will reveal narrowing of the lumen at the level of the third and fourth dorsal vertebra. Brief case reports of 7 operated cases are given. The patients ranged in age from 3 months to 20 months. Five had complete vascular rings, 1 an incomplete ring, and the last an abnormal course of the innominate artery. Thirteen patients who were not operated on were either asymptomatic, had symptoms of other conditions, or had mild symptoms from vascular rings. —E. Shabart

Silo-Filler's Disease. E. A. Cornelius* and E. H. Betlach. *Radiology*, February, 1960, 74: 232–238. (*Hermann Hosp., Houston, Texas)

Two cases of silo-filler's disease are reported and 12 others are reviewed. Two groups of cases are recognized: those in which severe illness develops immediately after exposure, and those in which early morbidity is followed by remission which, in turn, is succeeded by relapse. A history of exposure to an irritating gas arising from fresh silage is the most important single fact in diagnosis. Roentgenographic features are not diagnostic and should be correlated with the history. In the delayed group in relapse, roentgenographic changes may lag behind the clinical cycle. Pulmonary fibrosis and obstructive emphysema are possible complications in the delayed cases. Accurate evaluation requires pulmonary function tests and, possibly, lung biopsy. Adrenal cortical hormone has been of definite value in the delayed cases. Recommended precautions for farmers involve adequate silo ventilation and avoidance of silos where a yellowish-brown haze is evident or an irritating odor is detected. The simplest and safest solution is to stay out of the silo for at least 7 to 10 days after filling, with no exceptions for any reason whatever.—W. J. Steininger

Bilateral Synostosis of Seventh Rib and Scapula. A Case Report. J. M. Packer*, E. J. Harris, and R. P. Henderson. *Radiology*, February, 1960, 74: 289–290. (*Mississippi Baptist Hosp., Jackson)

A case is reported of bilateral, symmetric synostosis joining the seventh rib to the scapula at its inferior angle. This was an incidental finding and proved to be an isolated skeletal abnormality which was essentially asymptomatic. The only objective finding related to this condition was restriction of shoulder and upper extremity motion involving scapular movement (after authors' summary).—W. J. Steininger

Misleading Thoracic Roentgenograms: Cardiovascular Abnormalities That May Simulate Diseases of the Lungs, Bony Thorax, or Mediastinum. C. H. Hodgson*, J. A. Callahan, A. J. Bruwer, and A. H. Bulbulian. *AMA Arch Intern Med*, February, 1960, 105: 277–297. (*Mayo Clinic, Rochester, Minn.)

Roentgenograms of the thorax in certain cardiovascular conditions may simulate those associated with diseases of the lungs, bony thorax, or mediastinum. It is important to be aware of these similarities, which may be remarkable. Roentgenographic shadows may be produced that look very much like those characteristic of a different disease. The recognition of the real cause of these roentgenographic changes may allow treatment of an apparently hopeless condition or prevent an unnecessary operation. Examples of misleading roentgenograms in more than 20 cases are presented under the following categories: shadows produced by abnormal aortic contours, shadows suggesting intrathoracic tumor, shadows produced by intrathoracic fluid, and shadows of diverse origin and complexity.—W. J. Steininger

The Evaluation of Roentgen Therapy in the Management of Non-Resectable Carcinoma of the Lung. H. Barton*, G. McGranahan, Jr., and G. Jordan. *Dis Chest*, February, 1960, 37: 170–175. (*V.A. Hosp., Houston, Texas)

From April, 1949, through December, 1956, 225 men with histologic evidence of carcinoma of the lung received primary treatment: 39 were found to have a nonresectable tumor at the time of exploratory thoracotomy, while 186 were considered inoperable on the basis of metastases or bronchoscopic findings; 103 received roentgen therapy, while 122 had only supportive therapy. All were dead at the time of this study, the longest survival time being 42 months. Patients treated with roentgen rays lived an average of 5.2 months as compared to a survival of 1.9 months in the untreated cases. In treated patients, symptoms were partially or completely relieved in 70 per cent. —E. A. Rouff

Subpleural Lipomas. E. A. Ten Eyck*. *Radiology*, February, 1960, 74: 295–297. (*New York Hosp., N. Y., N. Y.)

On rare occasions, lipomas may occur beneath the parietal pleura and produce pulmonary densities. Except when they attain considerable size, with resultant pressure and interference with the contiguous cardiopulmonary structures, they are usually asymptomatic and are discovered on routine chest films. Preoperative diagnosis is unlikely unless there is an extrathoracic component. Lipomas should be considered in the differential diagnosis of pleural tumors. Three cases are reported.—W. J. Steininger

High-Energy Electrons in the Treatment of Malignant Tumors of the Thorax. E. M. Uhlmann* and J. Ovadia. *Radiology*, February, 1960, 74: 265–272. (*Michael Reese Hosp., Chicago, Ill.)

Sixteen cases of carcinoma of the esophagus and 22 cases of carcinoma of the bronchus were treated with high-speed electrons. By means of this modality, large doses of effective ionizing radiation can be applied to deep-seated tumors, with a relatively low integral dose to healthy tissue and consequent good tolerance by the patient. In 6 of the esophageal and 5 of the bronchial cancer cases, treatment was interrupted because of debility resulting from rapid extension of the primary carcinoma or metastatic spread. Eight of the 27 patients who received full courses of radiation are dead. To date, the survival times of the remainder range from 19 to less than 6 months. Even in patients who did not survive, the local response to therapy, confirmed at autopsy, was remarkable. None of the patients in this series was operable; most of them were debilitated and of advanced age. The outlook with other forms of radiation therapy was poor, and it was often questionable whether the patient could tolerate exposure to the necessary high doses of conventional roentgen therapy. Objective evaluation demonstrates the effectiveness of therapy with high-speed electrons in these advanced cancers. —W. J. Steininger

Roentgen Investigation of the Coronary Veins in Dogs. L. Di Guglielmo*, V. Baldrighi, C. Montemartini, and A. Schifino. *Acta Radiol (Stockh)*, March, 1960, 53: 191–200. (*U. of Pavia, Italy)

Although several papers dealing with the appearance of coronary artery filling in aortography have appeared in the literature, references to coronary vein filling are still infrequent. In 1957, the authors first reported their observations on the roentgen appearance of coronary veins in living dogs. This paper reports further results obtained under different conditions, and the anatomic features are summarized. Seventy-three dogs in which 223 thoracic aortographies were carried out were used in the experiments. The materials and methods are discussed in detail. Contrast filling of the veins appeared to bear some relationship to the degree of filling of the coronary arteries. However, good coronary artery filling did not always produce venous filling, probably due to the fact that the heart is equipped with an extensive capillary system. This allows for greater dispersal of the contrast media to the deep and superficial venous systems; by the time the contrast media reach the larger venous branches, the concentration will no longer be sufficient to render it roentgenographically. Epinephrine or epinephrine-like drugs administered to dogs make venous filling more frequent. —E. Shabart

CHEMOTHERAPY

The Incidence of Bacterial Resistance in Tuberculous Patients Admitted to the Hospital (in German). E. Dissmann* and E. Iglauer. *Tuberkulosearzt*, January, 1960, 14: 1–9. (*Landeskrankenhaus, Klagenfurt/Kärnten, Germany)

From 1955 to 1958, resistance to one or more drugs was found in more than 30 per cent of the tuberculous patients admitted to the hospital of this study. Resistance to more than one drug concerned predominantly the combination of streptomycin–isoniazid and, only very rarely, PAS. In untreated patients, the incidence of isoniazid-resistant bacilli rose continuously, while the number of infections with streptomycin-resistant strains showed a marked decline. —J. Haapanen

The Current Status of Chemotherapy of Systemic Fungal Disease. J. Utz* and A. Treger. *Ann Intern Med*, June, 1959, 51: 1220–1229. (*National Institutes of Health, Bethesda, Md.)

In actinomycotic infections, penicillin is still the most effective chemotherapy. Sulfadiazine in combination with an antimicrobial is recommended in cases of nocardiosis. Iodides and vaccine therapy have been the major therapeutic measures recommended in cases of aspergillosis. Iodides are also standard treatment for sporotrichosis, geotrichosis, and penicilliosis. There is little experience in the therapy of mucormycosis, and success has been achieved in a few cases by the surgical removal of the focus of infection, or by the control of an underlying disease, e.g., diabetes. In the treatment of histoplasmosis and

blastomycosis, amphotericin appears to be effective. Amphotericin, similarly, seems to be the best drug thus far for cryptococcosis. Amphotericin is least effective in systemic coccidioidomycosis and candidiasis, but worthy of use in the absence of other, more effective chemotherapy (after authors' summary).—T. H. NOEHREN

Treatment of Pneumonia in Children. L. S. TAITZ* and D. SLONE. *Brit Med J*, February 6, 1960, No. 5170: 398–399. (*Coronation Hosp., Johannesburg, South Africa)

Thirty-three infants and children with pneumonia were treated as outpatients with phenoxymethylpenicillin, and 87 per cent were clinically cured by this treatment. Among the 4 patients who failed to respond to oral penicillin, 2 showed initial improvement but later suffered relapses, 1 was proved to have whooping-cough bronchopneumonia, and 1 was later found to have active pulmonary tuberculosis. It is suggested that outpatient treatment with oral penicillin is the method of choice in cases of mild and moderately severe pneumonia.—E. A. RILEY

Treatment of Pulmonary Tuberculosis in Humans with the Thioamide of Alpha-Ethyl-Isonicotinic Acid (in Italian). L. PETRUCCIOLI*, M. PAGNI, and F. ROSSI. *Ann Med Sondalo*, September–October, 1959, 7: 265–285. (*Villaggio Sanatoriale, Sondalo, Italy)

Two patients with early, untreated pulmonary tuberculosis, and 14 patients with chronic, cavitary, antimicrobial-resistant cases of the disease were given the thioamide of alpha-ethyl-isonicotinic acid in a daily dosage of 1 gm. for 60 days. The efficacy of treatment was evaluated according to clinical, roentgenographic, bacteriologic, and immunologic criteria. The conclusions of this study were: (*1*) The drug showed an evident antimicrobial action in both groups of patients. (*2*) The best roentgenographic and bacteriologic results were obtained in the first 30–40 days of treatment. (*3*) The cutaneous tuberculin sensitivity increased in those patients with cavities and numerous bacilli after the first days of treatment. (*4*) Almost all of the patients had intestinal troubles due to drug intolerance, which improved with rectal administration of the thioamide. —I. ARCHETTI

Experience with Amphotericin in the Therapy of Histoplasmosis. J. YATES*, M. ATAY, H. LANGELUTTIG, C. BRASHER, and M. FURCOLOW. *Dis Chest*, February, 1960, 37: 144–156. (*Missouri State Sanatorium, Mt. Vernon)

The general principles of management found to be of value in pulmonary tuberculosis are useful in the therapy of histoplasmosis. Numerous antimicrobial and chemotherapeutic agents apparently effective *in vitro* have been found to be unsuitable for clinical use either because of toxicity or the low blood and tissue levels achieved. Amphotericin B is a polyene antimicrobial produced by a Streptomyces originally isolated from a soil sample obtained in South America. The oral and intramuscular routes are inadequate for effective therapy. It has negligible antibacterial effect but is a potent broad-spectrum antifungous agent. At present, it seems to be the most valuable agent available for the therapy of the deep mycoses. It is not an ideal antifungous agent because of the severity and frequency of its side effects, because it must be given intravenously daily for at least 8 weeks, and because it is primarily suppressive and not fungicidal in the great majority of cases. Results in 30 cases presented in this series bear out all of the factors enumerated. —E. A. ROUFF

Treatment of North American Blastomycosis with Amphotericin B. C. A. GORDEN* and W. B. STEWART. *Canad Med Ass J*, February 27, 1960, 82: 471–473. (*Victoria General Hosp., Halifax, Nova Scotia)

The first case of systemic North American blastomycosis to be recognized in Nova Scotia has been reported. A satisfactory recovery followed the use of amphotericin B; agranulocytosis developed during treatment (Authors' summary). —E. A. RILEY

Histologic and Bacteriologic Studies on Lymphatic Tuberculosis in the Guinea Pig Repeatedly Treated with Isoniazid (in Italian). C. PANA*, M. LUCCHESI, and G. STORNIELLO. *Ann Ist Forlanini*, No. 1, 1959, 19: 58–73. (*U. of Siena, Italy)

A group of 150 guinea pigs infected intradermally with *M. tuberculosis* were given isoniazid in 2 cycles of 2 months each, with an interval of 1 month between the cycles. The animals were killed 2, 3, and 4 months after treatment was stopped, gross anatomic examination was done, and specimens of lymph nodes and spleen were taken for histologic and bacteriologic study. On the basis of the results obtained, it was concluded that: (*a*) the second cycle of treatment did not change the effects already obtained with a single cycle in previous experiments; a decrease in the number of animals with tuberculous processes occurred with a single cycle of treatment; (*b*) bacteriologic sterility of the tuberculous processes was not certain, even in the presence of a histologic reaction of follicular hyperplasia; (*c*) the further administration of isoniazid caused a morphologic

reaction which was the expression of a high immunity developed by the few bacilli still present. —I. Archetti

Serotonin Degradation by Ceruloplasmin and Its Inhibition by Isoniazid and Iproniazid. C. J. D. Zarafonetis* and J. P. Kalas. *Amer J Med Sci*, February, 1960, 239: 203–206. (*Temple U. School of Med., Philadelphia, Penn.)

Postulating that fibrosis might result from a deranged interaction of serotinin-amine oxidase mechanisms at the tissue level, it was theorized that fibrosis would ensue whenever an excess serotonin effect was sustained over a sufficient period of time. This could result from a relative imbalance between the amount of serotonin present locally and the rate of its degradation. In this investigation, ceruloplasmin of human origin readily degraded serotonin at pH 7.4. Both isoniazid and iproniazid, however, strongly inhibited this pathway of serotonin oxidation. The psychopharmacologic and other clinical effects of iproniazid probably reflect not only its inhibition of monoamine oxidase activity, but also its inhibition of ceruloplasmin oxidation of serotonin. Isoniazid, on the other hand, appears only to inhibit the latter pathway. Possible implications of these findings with regard to a concept of fibrosis are discussed, with practical application in the field of wound healing, and in the greater fibrous proliferation noted about healed tubercles in isoniazid-treated subjects as compared with untreated or streptomycin-treated patients. —W. J. Steininger

First Results of the Antituberculous Activity of Kanamycin in the Experimental Animal (Guinea Pig) (in Italian). M. Lucchesi* and G. Storniello. *Ann Ist Forlanini*, No. 1, 1959, 19: 74–84. (*Istituto Carlo Forlanini, Rome, Italy)

Three groups of 20 guinea pigs each were infected intradermally with one of the following human mycobacteria: a strain susceptible to antimicrobials; an isoniazid-resistant strain; and a streptomycin-resistant strain. Ten guinea pigs in each group were given kanamycin subcutaneously in a daily dosage of 20 mg.; the other 10 served as controls. All of the animals were killed after 30 days of treatment, gross anatomic examination was performed, and the spleens, tributary lymph nodes, and specimens of the skin were obtained for morphologic study. In the animals of the first 2 groups and, less evidently, in those of the third group, a reaction with only limited necrosis was observed; these results were considered evidence of the activity of kanamycin on susceptible and isoniazid-resistant strains, while kanamycin was less active against streptomycin-resistant bacilli. In accordance with previous studies, it seemed that there was a correspondence between the *in vitro* and *in vivo* activities of kanamycin, in contrast with what was found earlier with cycloserine or pyrazinamide. —I. Archetti

The Effect of Para-Aminosalicylic Acid on Gastric Secretion (in German). I. Csergö, Gy. Bikich, Ö. Hevér*, and J. Borsay. *Tuberkulosearzt*, January, 1960, 14: 16–22. (*Szanatorium-utca 2, Budapest XII, Hungary)

The effects of a single intravenous infusion of PAS (24 gm. in 500 ml. of distilled water) on the secretion of hydrochloric acid, pepsin, and pepsinogen were studied in 26 tuberculous patients. A similar study was made in 9 tuberculous patients who received prolonged oral treatment with PAS. Gastric acidity was not affected either by a single infusion or by prolonged administration of PAS, but was lower in severe cases of tuberculosis. Both a single infusion and prolonged medication markedly reduced secretion of pepsin and pepsinogen as compared with the initial values. The possibility is discussed of an inhibitory action of PAS on enzyme activity in general. Substitution therapy with a mixture of organic acids and enzymes considerably increased PAS tolerance in 3 patients who had been unable to continue treatment because of gastrointestinal disturbances. —J. Haapanen

Is Para-Aminosalicylic Acid Taken Regularly by Patients as Prescribed? (in Japanese). G. Yamamoto*. *Clin Resp Org*, March, 1960, 15: 183–186. (*National Kyoto Sanatorium, Japan)

The writer used Ehrlich's and ferric chloride reactions on the urine of patients given PAS to ascertain whether the drug was taken regularly as prescribed, and found these tests very useful. He found that 17.5 per cent of the 277 patients examined did not take PAS at all, and 15.4 per cent of them took PAS secretly without permission of the physicians. Gastrointestinal disturbances due to large amounts of PAS prescribed over a long period were the chief reason the patients did not take the drug as prescribed. Those who took it without physician's order said they either used leftover supplies of PAS which had been prescribed previously, they were given PAS by other patients who did not take it, or that they bought it from drug stores themselves.—I. Tateno

A Clinical Study of the Protective Action of Pantothenic Acid Against the Ototoxicity of Streptomycin and Dihydrostreptomycin (in German). R. Ferlinz* and G. Huemer. *Tuberkulosearzt*,

January, 1960, 14: 9–15. (*Heilstätte Grafenhof, St. Veit (Salzburg), Austria)

A group of 77 children was treated with a mixture of streptomycin and dihydrostreptomycin in equal parts in an average daily dose ranging from 31 to 50 mg. per kg. of body weight. The same drugs in the pantothenate form were added to the regimen of 32 of these children. Audiometric and vestibular tests were performed before, during, and after the treatment. In none of these 77 children was there any evidence of a toxic lesion of the vestibular apparatus or the auditory mechanism. —J. Haapanen

A Study of a New Antifungal Substance, Tetrahydrofluorenone. L. G. Allgén* and A. Frisk. *Acta Med Scand*, March 10, 1960, 166: 161–174. (*Beckomberga Hosp., Stockholm, Sweden)

A study was made of the antimycotic effect of 1,2,3,4-tetrahydro-9-fluorenone (THF). A chemical method for determination of THF in serum and urine involves ultraviolet spectrophotometry after extraction with cyclohexane. Clinical trials with 40 patients from various hospitals in Sweden showed that oral THF therapy has a good effect on Candida infections of the mucous membranes. On oral administration or, preferably, in combination with instillation treatment (THF dilution 1:10,000), a good effect was also obtained in urinary tract infections and pleural empyemas caused by a secondary infection with fungi. With mycotic superinfections in the respiratory tract, good results were obtained in a few cases. With the exception of minor gastrointestinal complaints (nausea, diarrhea) in a few cases, no side effects were seen with THF therapy.—E. Dunner

*The Medical Letter**, May 27, 1960, 2: 41–44. (*136 East 57th St., New York 22, N. Y.)

Premarin®, a conjugated equine estrogen, in controlling spontaneous hemorrhage and in treatment of menopausal symptoms; comparison with synthetic estrogens such as diethylstilbestrol; sodium estrone sulfate (Amnestrogen®, Conestron®); and ethinyl estradiol (Estinyl®, Eticylol®, and Lynoral®). New appraisal of the new anti-fungal agent, griseofulvin (Griseofulvin®, Fulvicin®, Grifulvin®) in tinea captis and onychomycosis, and tinea pedis. Combinations of salicylates and para-aminobenzoic acid (Pabalate®, Pabasyl®, and Pabirin®) as analgesics and antirheumatic agents. Chlorpropamide (Diabinese®) in diabetes therapy.

The Medical Letter, June 10, 1960, 2: 45–48.

Birth control pills: norethynodrel with ethynylestradiol 3-methyl ether (Enovid®), and norethindrone (Norlutin®). Medroxyprogesterone acetate (Provera®), a new oral progestational agent, in menstrual disturbances and in threatened and habitual abortion. The new chemical skin-tanning preparations, such as Man-Tan®. Hot weather stability of antimicrobials.

PULMONARY PHYSIOLOGY

Changes in Forced Expiratory Volumes Throughout the Day. H. C. Lewinsohn*, L. H. Capel, and J. Smart. *Brit Med J*, February 13, 1960, No. 5171: 462–464. (*London Chest Hosp., England)

The forced expiratory volume (FEV) and forced vital capacity (FVC) were tested on 5 healthy men and 16 male patients with obstructive airway disease at fixed times throughout the day. At 6 a.m. the FEV and the FVC were lower than at any other time of the day both in healthy subjects and in patients. By 8 a.m. the mean increase in FEV was 2.9 per cent in the healthy subjects. By 9 a.m. it was 60 per cent and 36 per cent, respectively, in the patients with mild and severe obstructive airway disease. Similar changes were seen in the FVC. Relatively large spontaneous variations in the FEV and the FVC occurred between 9 a.m. and 5 p.m. in the patients. Possible explanations for these variations are discussed. —E. A. Riley

Respiratory Symptoms, Bronchitis, and Ventilatory Capacity in Men. H. C. Olsen* and J. C. Gilson. *Brit Med J*, February 13, 1960, No. 5171: 450–457. (*Rønne, Bornholm, Denmark)

Representative samples of men aged 55–64 in Rønne and in 2 agricultural areas in the United Kingdom are compared for prevalence of respiratory symptoms and ventilatory capacity. The prevalence of symptoms is significantly lower in Rønne. The mean indirect maximal breathing capacity (IMBC) is significantly higher in Rønne (106 l./min.) than in the U.K. samples (92 l./min.). The differences are not explicable on the basis of differences in height, weight, density of population, or atmospheric pollution. There are more non-smokers in Rønne and many fewer cigarette smokers than in the U.K. samples. Only in the small group of non-smokers are there no physiologic or clinical differences between the Rønne and U.K. samples. In Rønne there was significantly lower IMBC and poorer single-breath nitrogen clearance in the pure cigarette smokers than in the cigar smokers—despite similar tobacco consumptions. The results are discussed in relation to the problem of bronchitis and lung cancer. The practicability of international comparisons

of this type, using standardized criteria and tests, are demonstrated (after authors' summary). —E. A. Riley

Cardiopulmonary Physiological Responses to Heavy Exercise in Patients with Anemia. B. J. Sproule*, S. H. Mitchell, and W. F. Miller. *J Clin Invest*, February, 1960, 39: 378–388. (*U. of Texas, S. W. Med. School, Dallas)

The cardiopulmonary responses of 9 male patients with various types of anemia were compared with those of a larger number of normal subjects during heavy treadmill exercise. At rest, anemic individuals are able to handle the delivery of oxygen and transport of CO_2 in relatively adequate fashion. Compensation was achieved by several means. During strenuous exercise, these hemodynamic adjustments were insufficient to prevent a marked depression of both oxygen intake and carbon dioxide production in comparison with those found in normal individuals exercising at comparable levels. Despite the evidence for an increase in anaerobic metabolism in anemic subjects, and in spite of the reduced buffering capacity reflected in the resting state by an increased A-V pH difference, the arterial and venous pH was not lower than normal. The absence of a greatly exaggerated arteriovenous pH difference during vigorous exercise suggests that there may be a lag in the release from the tissues of acid metabolites arising from anaerobic glycolysis in anemic patients. Nevertheless, they evidenced no more symptomatic distress than did normal people during these same periods of violent exercise.—E. Dunner

A Clinical Consideration of Cor Pulmonale. R. M. Harvey* and M. I. Ferrer. *Circulation*, February, 1960, 21: 236–255. (Columbia U., College of Physicians and Surgeons, N. Y., N. Y.)

There are only 2 basic pathophysiologic mechanisms that compromise the heart and lead to cor pulmonale: (*1*) alveolar hypoventilation with moderate or severe anoxia and hypercapnia leading to pulmonary vasoconstriction, hypervolemia, and increased cardiac output, and (*2*) anatomic curtailment of the pulmonary vascular bed, or a combination of these factors. Among the diseases that produce alveolar hypoventilation are emphysema, silicosis, neuromuscular diseases, structural deformities of the chest cage, obesity, cystic fibrosis of the pancreas, and bronchiolitis. Conditions that produce cor pulmonale by reduction of the pulmonary vascular bed include multiple pulmonary emboli and the syndrome of alveolar-capillary block. Under the latter general heading come the diseases that produce lesions in the alveolar-capillary membrane and are characterized by difficulty of oxygen diffusion: beryllosis, Boeck's sarcoid, scleroderma, and certain granulomatous lesions and reticular fibroses of undetermined etiology. Therapy for the various specific disease processes responsible for cor pulmonale is outlined.—W. J. Steininger

A Study on the Intrapulmonary Mixing of Gases in Silicotic and Emphysematous Patients (in Italian). E. Sartorelli*, A. Grieco, and S. Zedda. *Med Lavoro*, December, 1959, 50: 766–780. (*Cl. Lavoro, U. of Milan, Italy)

A comparative study was made of the intrapulmonary mixing of gases in 15 normal young and adult men, 25 patients with different degrees of emphysema, and 36 with silicosis in different stages of evolution. The methods were based upon the analysis of the curves of the nitrogen pulmonary clearance during open-circuit pure oxygen breathing, using the nitrogen fast-analyzer "Waters-mod. A-6." From this comparison it was clear that in most of the emphysematous patients and in those with more advanced silicosis (types 2n-3n and A-B of the Geneva classification) there was uneven alveolar ventilation. This was revealed by an increase in the length of time of mixing; by the constant presence of 3 different lung sections, each ventilated at a different rate; and, finally, by the alterations in volumetric ratio between the various lung sections. In most of the other silicotic patients the pattern of mixing was almost normal. The uneven ventilation in advanced silicosis is, therefore, considered an important factor in the pathogenesis of the ventilatory insufficiency characteristic of the disease. —I. Archetti

Hyperventilation with Oxygen. A Possible Cause of Cerebral Hypoxia. K. Sugioka* and D. Davis. *Anesthesiology*, March-April, 1960, 21: 135–143. (*U. of North Carolina School of Med., Chapel Hill)

An oxygen electrode was used to measure the actual brain tissue oxygen tension in an effort to establish the possibility that actual cerebral hypoxia occurs during decreased cerebral blood flow with active and passive hyperventilation. A brief history is given on the development of such an electrode. The method of study is described in detail on the use of a miniature electrode developed by Liston of the Beckman Instrument Company. The amplifier for the electrode is the Beckman/Spinco Model 160. Quantitative direct measurement of cerebral Po_2 in anesthetized dogs was recorded. A 90 per cent rise in cerebral Po_2 was obtained during inspiration of pure oxygen by the spontaneously breathing dog. Hyper-

ventilation, with either room air or 100 per cent oxygen, caused a drop of cerebral Po_2 from 8–15 mm. to 3–5 mm. A correlation exists between low alveolar carbon dioxide and low cerebral Po_2. When carbon dioxide is added to the inspired gases during hyperventilation, a rise in cerebral Po_2 occurs and a prompt fall to low levels again occurs when the carbon dioxide is removed. —E. Shabart

Evaluation of the Slope-Volume Method as an Index of Pulmonary Blood Volume. Y. Wang*, J. T. Shepherd, and R. J. Marshall. *J Clin Invest*, March, 1960, 39: 466–472. (*Mayo Clinic, Rochester, Minn.)

Studies were carried out to test the validity of the Newman slope-volume method as an index or measurement of the volume of blood in the lungs. Indocyanine (cardio-green) dye was injected into the pulmonary artery of the dog, and indicator dilution curves were inscribed at the aortic root using a densitometer with a high frequency response. The Stewart-Hamilton method was used to derive the volume of blood in the lungs and the chambers of the left side of the heart; the Newman method was used to calculate the slope volume. With the assumption that the Stewart-Hamilton method is valid, it appears that the slope volume neither gives a measurement of the volume of blood in the lungs nor reflects the magnitude of changes induced therein. —E. Dunner

The Effect of Carbon Dioxide on the Pulmonary Circulation. F. Manfredi* and H. O. Sieker. *J Clin Invest*, February, 1960, 39: 295–301. (*Duke U. School of Med., Durham, N. C.)

The effect of alveolar and blood carbon dioxide tension changes on the pulmonary vascular dynamics has been studied in 12 dogs, using the left lower lobe isolated and mechanically ventilated and perfused. Corollary observations have also been made for alveolar and blood oxygen tension changes. Increase in alveolar and pulmonary venous carbon dioxide tension, whereby the pCO_2 gradient between pulmonary arterial and pulmonary venous blood was lowered, resulted in a local elevation of pulmonary vascular resistance, probably from pulmonary arteriolar constriction. No significant hemodynamic variation occurred with high or low carbon dioxide tensions in the pulmonary artery, vein, or alveoli of the explored lung segment so long as a large pulmonary arteriovenous gradient for pCO_2 was maintained. Decrease in alveolar and pulmonary venous oxygen tension, whereby the oxygen tension gradient between pulmonary arterial and venous blood was lowered, resulted also in local elevation of pulmonary vascular resistance. Perfusion of the isolated lobe with hypoxic blood produced no change in local pulmonary vascular resistance. It is postulated that a local homeostatic mechanism exists, probably similar to that described for oxygen, which can divert blood from poorly ventilated alveoli that retain carbon dioxide to adequately ventilated segments of the lung. —E. Dunner

Some Effects of Ankylosing Spondylitis on Pulmonary Gas Exchange. A. D. Renzetti, Jr.*, W. Nicholas, R. E. Dutton, Jr., and L. Jivoff. *New Engl J Med*, February 4, 1960, 262: 215–218. (*V. A. Hosp., Syracuse, New York)

Studies of pulmonary function in patients with ankylosing spondylitis have established that the vital capacity is frequently reduced and that the maximal ventilatory capacity is decreased proportionately less than the vital capacity. The present study indicates that hyperventilation and abnormalities of alveolar ventilation-perfusion relations may also be present in patients with ankylosing spondylitis. These abnormalities gave rise to mild arterial hypoxia and an increase in the physiologic dead space. Twelve patients were studied who had clinical and roentgenographic evidence of ankylosing spondylitis but no lung or heart disease. In comparison with normal respiration, the spondylitic process leads to a relative decrease in ventilation in the upper part of the lung, whereas increased excursions of the diaphragm lead to a relative increase in ventilation in the lower-lung regions. It is suggested that the hyperventilation and pulmonary gas exchange defects might result from this relative overexpansion of the lower and underexpansion of the upper portions of the lung. The vital capacity may well be used as an objective criterion for the evaluation of the degree of ankylosing joint disease in the thoracic spine.—M. J. Small

The Relationship of the Hyperinflated Lung to Obstructive Pulmonary Disease. N. M. Lefcoe* and G. Goodall-Copestake. *Canad Med Ass J*, February 27, 1960, 82: 464–467. (*U. of Western Ontario, Canada)

A study correlating pulmonary function studies and the roentgenographic diagnosis of emphysema was carried out on 139 patients. The timed vital capacity was used as an index of obstruction. Among 31 patients with a timed vital capacity of less than 58 per cent in the first second, 5 had negative films, 4 were read as "suggestive of emphysema," and 22 as "definite emphysema." This is an over-all correlation of 84 per cent. Among 47 patients with a timed vital capacity of more than 58 per cent, the films were read as nor-

mal in 85 per cent of the cases. Fifty-two cases were not included because of the presence of a contracted lobe or segment which completely destroyed the correlation.—E. A. RILEY

Acta Med Scand, February 17, 1960, 166: pp. 107–124:

Mechanical Properties of the Lungs During Exercise in Patients with Cardiac or Pulmonary Disease. O. NISELL*. Pp. 107–112. (*Serafimerlasarettet, Stockholm, Sweden)

In 8 patients with heart disease, exercise reduced the resistance by an average of 27 per cent from 4.6 cm. H_2O/L/sec., and the impedance by an average of 10 per cent from 6.6 cm. H_2O/L/sec. In 7 patients with lung disease, the resistance increased during exercise by an average of 16 per cent, while the corresponding increase in impedance was 19 per cent. An effect similar to that of exercise accompanied voluntary hyperventilation. Compliance decreased significantly during exercise in 4 cardiac patients.

The Respiratory Work and Pressure during Exercise, and Their Relation to Dyspnea. Pp. 113–119.

The pressure fluctuation and work of breathing for the lungs increased by an average of 1.1–4.0 cm. H_2O and 25–161 liter-centimeters H_2O per minute with an exercise increase of 100 kg. per minute in 18 subjects, most of whom had pulmonary or cardiac disease. The magnitude of the pressure value seemed to be directly related to the pressure amplitude at rest. The relation between pressure and exercise appeared to be more linear than that between respiratory work and exercise. At the highest exercise level the pressure averaged 15.0 cm. H_2O (coefficient of variation (c.v.) 37 per cent), the resistive work 253 liter-centimeters H_2O per minute (c.v. 80 per cent), and the inspiratory work 256 liter-centimeters H_2O per minute (c.v. 60 per cent). The respiratory pressure showed a closer relation to dyspnea and ventilatory effort than did the respiratory work.

Factors Determining the Respiratory Pressure and the Onset of Dyspnea. Pp. 121–124.

The respiratory pressure fluctuations in the esophagus were compared in subjects (most of whom had pulmonary or cardiac disease) with the pressure calculated by means of an alternating circuit equation. The close agreement suggests that the pressure amplitude is proportional to both the flow and the impedance of breathing. The pressure amplitude changed in each subject approximately linearly with the flow between rest, exercise, and hyperventilation. High pressure amplitudes and, hence, dyspnea are associated with high flow, high resistance, or low compliance. —E. DUNNER

A Study of Etiologic Factors in So-Called Primary Pulmonary Hypertension. A. J. RAWSON* and H. M. WOSKE. *AMA Arch Intern Med*, February, 1960, 105: 233–243. (*U. of Pennsylvania Hosp., Philadelphia)

Four patients with so-called primary pulmonary hypertension (PPH) were studied clinically and at autopsy. The histologic appearance of the lungs was similar in all cases, consisting essentially of marked intimal cellular proliferation in the small muscular arteries and arterioles, with severe vascular stenosis. Two patients had arthritis and Raynaud's phenomena. One patient had extrapulmonary lesions suggestive of a "collagen" disease. Two patients had close relatives who had arthritis and Raynaud's phenomena. Review of well-documented published cases shows a higher than normal incidence of arthritis (8 per cent), Raynaud's phenomena (21 per cent), and lesions suggestive of "collagen" disease (10 per cent) in patients with PPH. It is suggested that many, if not most, cases of PPH may be related to the "collagen" group of diseases (after authors' summary).—W. J. STEININGER

Roentgenographic Determination of Total Lung Capacity. H. BARNHARD*, J. PIERCE, J. JOYCE, and J. BATES. *Amer J Med*, January, 1960, 28: 51–60. (*Hahnemann Med. College, Philadelphia, Penn.)

A roentgenographic method for the determination of total lung capacity is described. This method requires postero-anterior and lateral views of the chest and involves principally the summation of a series of elliptical cylindroids into which the lungs are divided. The method is simple, rapid, and accurate. The roentgenographic method was compared with a conventional physiologic measurement of total lung capacity in 74 persons. A high degree of correlation was found in healthy young subjects, healthy old subjects, and patients with congestive heart failure. A significantly lower correlation was found in patients with emphysema. The mean total lung capacity in the emphysematous group was 0.81 L. more by the roentgenographic method than by the dilution technique. This discrepancy appears to result from errors in the measurement of the residual volume by the nitrogen dilution method. It illustrates further that there is a more severe alteration of the volume elastic properties of the lungs in emphysema than was previously indicated (after authors' summary).—T. H. NOEHREN

Myxoedema Coma and CO_2-Retention. P. Nordqvist*, K.-G. Dhunér, K. Stenberg, and G. Örndahl. *Acta Med Scand*, March 10, 1960, 166: 189–194. (*Sahlgren's Hosp., Gothenburg, Sweden)

It is emphasized that CO_2-narcosis must be considered as an explanation of myxedema coma, and careful respiratory treatment is of importance not only in connection with coma but also later during the course. It was found that the most reliable means of recording the activity of triiodothyronine was to measure the oxygen consumption.—E. Dunner

Pressure-Flow Characteristics of Needles Suggested for Transtracheal Resuscitation. T. P. Bougas* and C. D. Cook. *New Engl J Med*, March 10, 1960, 262: 511–513. (*Harvard Med. School, Boston, Mass.)

Resuscitation of patients with upper-airway obstruction by means of small-bore needles inserted percutaneously into the trachea has been suggested. This study reports the pressure-flow characteristics of needles that have been designed for this type of resuscitation. It is concluded that, although a transtracheal needle may be better than no airway at all and may under certain circumstances be useful (as in the very small infant, the largest needle being used), it probably cannot provide adequate ventilation in the spontaneously breathing person without extremely exhausting effort on the part of the patient. If the only aim is to provide diffusion respiration, it is possible to supply an adequate amount of oxygen but, if high flow rates are used, dangerous pressures are necessary. In the rare situation in which the upper airway is totally obstructed, distention and rupture of the lungs appear to be real possibilities. It is believed that the technique of transtracheal resuscitation with a needle may delay the establishment of an adequate airway (which would be established better either with an endotracheal tube or via a tracheostomy) and, in addition, provide a false sense of security. In any event, its usefulness for diffusion respiration rather than for to-and-fro respiration should be fully appreciated by persons employing the transtracheal needle for resuscitation of obstructed patients.—M. J. Small

Simplification of Haldane's Apparatus for Measuring CO_2 Concentration in Respired Cases in Clinical Practice. E. J. M. Campbell*. *Brit Med J*, February 13, 1960, No. 5171: 457–458. (*Middlesex Hosp., London, England)

A simplified Haldane's apparatus is described for measuring CO_2 concentration in respired gases. This adaptation is suitable for clinical practice. Serial analyses were reproducible to within ±0.05 per cent, and comparison with standard apparatuses gave agreement usually within ±0.05 per cent and never beyond ±0.1 per cent.—E. A. Riley

Simple Rapid Methods of Estimating Arterial and Mixed Venous pCO_2. E. J. M. Campbell* and J. B. L. Howell. *Brit Med J*, February 13, 1960, No. 5171: 458–462. (*Middlesex Hosp., London, England)

The physiologic significance of the measurement of arterial pCO_2 is summarized and previous methods are reviewed. Collier's rebreathing method for the estimation of the mixed venous and arterial CO_2 tensions is outlined. A simplification of Collier's method, eliminating the necessity for a continuous record of CO_2 concentration, is described. An evaluation of the method showing that the accuracy is to within ±3 mm. Hg. is described in patients with various disorders of CO_2 and pH regulation. Simple routines for the estimation of pCO_2 are described for use both with and without continuous analysis of CO_2 (after authors' summary).—E. A. Riley

MICROBIOLOGY AND IMMUNOLOGY

Studies on Fractions of Methanol Extracts of Tubercle Bacilli. II. Toxic and Allergenic Properties of Fractions Employed as Antituberculous Vaccine. C. A. Williams, Jr.* *J Exper Med*, March, 1960, 111: 369–386. (*Rockefeller Institute, N. Y., N. Y.)

A previous report from this laboratory has described the ability of partially purified fractions of methanol-extracted tubercle bacilli to induce increased resistance of mice to experimental tuberculosis, and suggests that at least two mechanisms are possibly involved in immunity. The present investigation presents studies of the toxic and allergenic properties of vaccines chemically derived from *Mycobacterium tuberculosis* H37Rv.

Toxicity of the various preparations was determined by the production of inflammatory skin reactions in guinea pigs, induction of weight loss in mice after intraperitoneal injection, and depression of resistance to staphylococcal infections in mice. Allergenicity was determined by the ability of fractions to evoke a hypersensitive skin response in guinea pigs previously sensitized with whole tubercle bacilli, and the capacity of fractions to induce hypersensitivity when used as sensitizing antigens. Fraction FI, a preparation precipitated from the methanolic extracted H37Rv by slow concentration at 45°C., was both toxic and allergenic. The chemical treatment of FI with ethanol and saline yielded a water-soluble

preparation, FI-S, devoid of toxicity and allergenicity, and a precipitate, FI-P, retaining these properties. These findings were of particular interest since the soluble fraction, FI-S, had been demonstrated in the previous report to be the most active single substance in producing resistance to experimental tuberculous infection in mice.—C. H. PIERCE

The Niacin Test in Tubercle Bacilli (in Japanese). T. TOMODA*, N. KANEDA, N. TSUCHIYA, and Y. AKIYAMA. *Clin Resp Organs*, February, 1960, 15: 96–98. (*Osaka Med. College, Japan)

The niacin test was used on known types of human, avian, and bovine tubercle bacilli and the test was positive only in the human type. The test was also used on 137 strains of tubercle bacilli isolated from patients' sputum, and was positive in all except 1 specimen which was a strain of unclassified mycobacteria. Isoniazid resistance did not have any influence on the result of the niacin test. The test was considered useful in differentiating human bacilli from other types, and also for differentiating known from unclassified mycobacteria.—I. TATENO

Studies on the Virulence of Yellow Bacilli (the So-called Atypical (Unclassified) Acid-fast Bacilli) (in Japanese). K. OSHIMA*. *Kekkaku*, March, 1960, 35: 201–205. (*Toneyama National Hosp., Osaka, Japan)

The behavior of unclassified acid-fast bacilli in mice was compared with that of nonpathogenic mycobacteria (*M. phlei* and *M. butyricum*) and other mycobacteria by the quantitative culture of the homogenized material of the whole bodies of mice. The unclassified acid-fast bacilli used in the experiment were 8 strains from patients in the author's sanatorium and 3 strains sent from the U.S.A. (*1*) The viable units of nonpathogenic mycobacteria decreased rapidly following inoculation, and viable bacilli were scarcely recoverable after 2 to 4 weeks of infection. (*2*) The unclassified acid-fast bacilli isolated by the author and the strains from the U. S. behaved similarly. Their behavior in the bodies of mice could be divided into 3 types: those which showed an initial increase, similar to the H37Rv strain; those which maintained the same number of viable units for 4 to 6 weeks as they did at the time of infection—a pattern similar to that of low-virulence Vole bacillus; and those which showed a gradual decrease of viable units, as in the case of strain H37Ra.—I. TATENO

EXPERIMENTAL PATHOLOGY

Dispersion and Viability of BCG after Intradermal Injection in the Guinea Pig. T. M. VOGELSANG* and P. WETTELAND. *Acta Path Microbiol Scand*, Fasc. 2, 1960, 48: 169–175. (*U. of Bergen School of Med., Norway)

Intradermal injection of BCG gives dispersion and viability similar to those obtained by subcutaneous inoculation of a corresponding dose. —E. DUNNER

Glass Dust: A Study of Its Biologic Effects. P. GROSS*, M. WESTRICK, and J. MCNERNEY. *AMA Arch Industr Health*, January, 1960, 21: 10–23. (*Mellon Institute, Pittsburgh, Penn.)

A study was made of the biologic effects of glass dust upon the conjunctiva, the gastrointestinal tract, and the lungs of experimental animals. The pulmonary changes in guinea pigs exposed to fine glass dust for one year, and those in rats either exposed to the same dust or given injections intratracheally with it, were minimal in character and consisted only of small focal alveolar dust-cell collections without fibrosis. In the pulmonary lymph nodes there were also focal intracellular glass-dust deposits which were likewise not associated with reactive fibrosis. There was no bronchial disease attributable to the dust.—T. H. NOEHREN

The Pulmonary Response to a Proteinaceous Dust. P. GROSS*, M. WESTRICK, and J. MCNERNEY. *AMA Arch Industr Health*, June, 1959, 20: 477–488. (*Industrial Hygiene Foundation, Pittsburgh, Penn.)

Guinea pigs were given a preliminary injection of boiled skimmed milk, and exposed for a maximum of 12 months in an inhalation chamber to a dust derived from an aerosol of boiled skimmed milk plus kaolin. Control guinea pigs were exposed to a similar concentration of kaolin dust alone, in an identical chamber, for 1 year. Two other comparable groups of guinea pigs, exposed to quartz dust and glass dust, respectively, under similar conditions for 1 year, served as additional controls. Two observations appear to be unique, and suggest that they are a response to the presence of a foreign protein in the animals: a proliferative and obliterative alveolitis, concentrated mainly along scattered bronchioles and their peripheral connecting structures, associated with an unusual fine-meshed reticulin network; and isolated granulomatous foci, with central necrosis and eosinophilic infiltration. The role that allergy plays in the production of these lesions has not been established (after authors' summary).
—T. H. NOEHREN

The Effect of the Intestinal Flora on the Growth Rate of Mice and on Their Susceptibility to Experimental Infections. R. J. DUBOS* and R. W. SCHAEDLER. *J Exper Med*, March, 1960, 111: 407–417. (*Rockefeller Institute, N. Y., N.Y.)

During recent years, colonies of laboratory animals free of certain pathogenic agents have been established. The present report describes comparative studies of two mouse colonies, the standard Rockefeller Swiss (SS) and the Nelson-Collins Swiss (NCS). The latter colony was initially derived by Caesarian section from the SS strain and has since been maintained free of common mouse pathogens. In comparison with SS mice, the NCS animals grew more rapidly when fed complete diets, and gained weight on deficient diets. NCS mice were more susceptible to experimental bacterial infections with *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Mycobacterium fortuitum*, and *Mycobacterium tuberculosis* var. *bovis*. In contrast, they were more resistant than SS mice to the lethal effect of endotoxins from *Klebsiella pneumoniae* and *Escherichia coli*. However, NCS animals responded to small amounts of endotoxin by a marked increase in susceptibility to staphylococcal infection.

Bacteriologic studies of the intestinal flora revealed the coliform group of microorganisms to be present in SS mice, but absent in NCS animals. Lactobacilli, enterococci, and small numbers of unidentified Gram-negative bacilli comprised the fecal microbial population of NCS mice. When animals of the latter colony were contaminated either by contact or by feeding with a culture of *E. coli* isolated from the intestinal tract of SS mice, they responded as did the original mouse colony in respect to weight gain, experimental bacterial infections, and the lethal effect of endotoxins.—C. H. PIERCE

On the Correlation between Positive Reactions to Serum Colloidal Lability Tests and the Electrophoretic Serum Globulin Fractions in Tuberculous Patients (in Italian). R. ITALIA* and C. SACERDOTI. *Minerva Med*, No. 100, 1959, 50: 4136–4145. (U. of Milan, Italy)

The Kunkel, Maclagan, and Wunderly-Wuhrmann serum lability tests were performed on serum specimens from 363 patients with primary or post-primary pulmonary tuberculosis (the Wunderly-Wuhrmann test was done only on 287 specimens), without distinction as to the age and sex of the patients or the clinical form of the disease, and their correlation with the electrophoretic serum protein pattern was studied by the calculation of the correlation indices. According to the results, the 3 tests were never able to reveal hyper-alpha-2-globulinemia which, with hyper-gammaglobulinemia, was considered 1 of the 2 elements frequently found in tuberculosis. The Kunkel and Maclagan tests were often negative and, on the contrary, were positive many times in those patients with either normal or hypo-alpha-2-globulinemia. None of the tests seemed to be useful in determining hyper-alpha-1-globulinemia and hyper-alpha-globulinemia, while all 3 reactions—and especially the Maclagan and the Kunkel tests—were found to be electively sensitive in revealing hyper-gammaglobulinemia. —I. ARCHETTI

Pleural Fluid Glucose with Special Reference to Its Concentration in Rheumatoid Pleurisy with Effusion. C. CARR* and M. POWER. *Dis Chest*, March, 1960, 37: 321–324. (*Mayo Clinic, Rochester, Minnesota)

The measurement of glucose in pleural fluid is not of great clinical value, as neither low nor high concentrations are diagnostic of any specific disease. A range of less than 5 to 17 mg. per 100 ml. was found in 6 patients who had rheumatoid arthritis with rheumatoid pleurisy and effusion. Fifty-four other cases of malignancy, congestive heart failure, pulmonary infarction, and some inflammatory and traumatic conditions had glucose fluid levels from 30 mg. to more than 120 mg. —E. A. ROUFF

Pulmonary Hyaline Membranes: A Study of the Infant Disease and Experimental Hyaline Membranes Induced Pharmacologically. S. BUCKINGHAM* and S. C. SOMMERS. *AMA J Dis Child*, February, 1960, 99: 216–227. (*Boston City Hosp., Mass.)

The lungs of 25 infants with hyaline membrane disease were studied histologically and, in part, by ultraviolet microscopy. Hypersecretory changes occurred in the terminal bronchioles and alveolar lining cells. Desoxyribonucleic acid found incorporated in the membranes appeared to have been leached out of the alveolar lining cells. Experimental pulmonary hyaline membrane formation was studied in mice with the use of high oxygen concentrations and various pharmacologic agents that may be related to suspected pathogenetic mechanisms. Mice were found to be resistant to concentrated oxygen, but showed an enhanced response and many hyaline membranes after atropine, Compound 48-80, pertussis-sensitization, and cortisone. Tryptamine did not confer protection against membrane formation in these experiments. It is suggested that the secretory products of the respiratory and alveolar epithelium participate in the formation of the hyaline membranes, and that these changes may reflect autonomic nervous system dysfunction (after authors' summary).—M. J. SMALL

PUBLIC HEALTH AND EPIDEMIOLOGY

B.C.G. and Vole Bacillus Vaccines in the Prevention of Tuberculosis in Adolescents. Medical Research Council*. *Brit Med J*, September 12, 1959, No. 5149: 379–396. (*London, England)

A controlled clinical trial of BCG and vole bacillus vaccines in the prevention of tuberculosis in England started in 1950 and is still in progress. During the first 5-year period the annual incidence of tuberculosis in the BCG-vaccinated group was 0.38 per 1,000, compared to 2.29 per 1,000 among those in the tuberculin-negative unvaccinated group who were admitted concurrently; this represents a reduction, attributable to vaccination, of 83 per cent. Over the same period, the annual incidence of tuberculosis in the vole-bacillus-vaccinated group was 0.33 per 1,000, compared to 2.62 per 1,000 among those admitted concurrently to the tuberculin-negative unvaccinated group; this represents a protection of 87 per cent. The degree of protection was similar for pulmonary tuberculosis, for tuberculous pleural effusion, and for hilar gland enlargement (in association with other lesions). On the other hand, since 4 cases of tuberculous meningitis and 4 of miliary tuberculosis were found among the negative unvaccinated participants, but none among those who were vaccinated, the degree of protection may have been greater for these forms. There is now also a suggestion that the lesions in the vaccinated cases were less extensive (both on the first abnormal roentgenogram and at their maximal extent) and less severe (as judged by the action taken by the clinician) than those in the negative unvaccinated cases. In other words, the degree of protection for the more extensive and severe lesions was certainly as great as, and may even have been greater than, that for the less extensive and severe lesions (authors' summary in part).—E. A. Riley

A Single Tuberculin Test for Epidemiological Use: A Comparison of the Mantoux and Heaf Tests. A Report to the Research Committee of the British Tuberculosis Association by Their Tuberculin Sub-Committee. *Tubercle*, October, 1959, 40: 317–335.

Intracutaneous (Mantoux 5-TU) and multiple-puncture (Heaf) tuberculin tests were made at the same time on opposite arms of 3,640 persons, and the reactions were read 3, 7, and 10 days later. Those with negative reactions to the intracutaneous 5-TU test at the 3- and 7-day readings were retested with 100 TU and the reactions were read 3 days later. Regarding 6 mm. induration or more as a positive reaction, the intracutaneous 5-TU test showed that 45.5 per cent of the population were positive after 3 days, 45.6 per cent after 7 days, and 24.1 per cent after 10 days, while for the multiple-puncture test the corresponding percentages positive were 74.3 per cent, 78.0 per cent, and 78.3 per cent. The intracutaneous 5-TU test, followed if negative by 100 TU, showed 78.5 per cent of the population to be positive after 3 days; thus, the multiple-puncture test read at 7 days gave results closely similar to those of the two-stage intracutaneous test read at 3 days. For epidemiologic use, the multiple-puncture test will in most circumstances be preferred to the intracutaneous test with 5 TU because of its greater sensitivity and ease of performance and reading. —M. J. Small

Field Trial of Influenza Virus Vaccine in Patients with Chronic Bronchitis During the Winter 1957-8. British Medical Research Council*. *Brit Med J*, November 7, 1959, No. 5147: 899–905. (*London, England)

A trial is reported in which the relative effects were studied of 3 influenza virus vaccines on groups of patients suffering from chronic bronchitis. Some patients were inoculated in September–October, 1957—somewhat late for the Asian wave of influenza—and others in December, 1957. Although protection from influenza was provided in the earlier groups of male patients given "Asian" vaccine, female patients did not appear to be similarly safeguarded. Possible reasons for this were discussed. No significant differences were observed between the attack-rates of bronchitis or other respiratory illnesses in the 3 inoculation groups. Finally, no significant differences in mortality were demonstrated between the several groups (after author's summary). —E. A. Riley

Long-term Postoperative Prognosis of Mine Workers with Tuberculosis (in Japanese). T. Kinoshita*, M. Yamada, and K. Suzuki. *Jap J Clin Tuberc*, December, 1959, 18: 882–884. (*Miike Mine Hosp., Fukuoka, Japan)

Studies were made on 186 mine workers (64 worked in and 122 worked out of the pit) who had undergone various types of surgery for pulmonary tuberculosis. They included 86 cases of thoracoplasty, 10 of plombage, 20 of thoracoplasty and plombage, 56 of resection, and 14 of resection and thoracoplasty. The relapse rate was significantly less in those who had resection than in those who had collapse therapy. The relapse was less the longer the postoperative treatment in hospital. At least 1 year of rest after lobectomy and 1½ years after thoracoplasty were recommended. Those who undergo thoracoplasty should be care

fully observed for a very long time after they return to work. Lobectomy followed by thoracoplasty appeared to be better than lobectomy alone. It was not concluded that those who worked in the pit were more liable to have relapses than those who worked out of the pit.—I. TATENO

Studies on the Correlation between the Viability of BCG Vaccine, the Vaccinal Lesion, and the Tuberculin Allergy Induced by Vaccination in Humans. Report I (in Japanese). Y. OBAYASHI*, T. SAWADA, G. KIKUCHI, C. CHO, J. KAWASAKI, Y. INOUE, and S. OTA. *Kekkaku*, December, 1959, 34: 866–869. (* Institute of Kekkaku Yobokai, Kiyose, Tokyo, Japan)

The correlation was investigated in humans between the number of viable bacilli in BCG vaccine and the intensity of tuberculin allergy after vaccination. Twenty-eight different lots of dried vaccine (0.05 mg.) were inoculated into 3,028 school children and the tuberculin reactions were tested with OT 1, 3-to-4, and 12 months after vaccination. Forty-five different lots of vaccine were given to 1,211 school children in the second experiment, and the tuberculin reactions were tested with OT and PPD (received from WHO) 4 and 12 months after vaccination. All of the children had never received BCG vaccination previously and were tuberculin negative. The mean diameter of redness and induration was taken as an indication of the intensity of reaction to OT and PPD, respectively. Significant positive correlation between the number of viable bacilli in the BCG vaccine and the intensity of the tuberculin reaction tested with either OT or PPD after vaccination was demonstrated in both experiments, and remained demonstrable for a year after vaccination.—I. TATENO

Studies of Acceleration of the Tuberculin Reaction when the Tuberculin Test is Applied Repeatedly. Report II (in Japanese). H. BACHI*. *Kekkaku*, December, 1959, 34: 838–843. (*Gumma U. School of Med., Maebashi, Japan)

Accelerated or delayed tuberculin reactions have recently attracted the attention of workers in tuberculosis prevention campaigns because the incidence of such reactions increased with increased tuberculin testing in campaign populations. The writer injected 0.1 ml. of 1:2,000 OT at intervals of 2 months into the backs of patients who were expected to undergo thoracic surgery, and had a piece of skin resected at the time of operation. The last injection was made 2 to 72 hours before. At the skin sites where only 1 tuberculin injection had been made, the inflammatory reaction was weak at the early stage and stronger at 48 hours, whereas, when the tuberculin had been injected 2 or 3 times before operation, the inflammatory reaction was stronger at the early stages and weak at 48 hours.—I. TATENO

Radiation Control at the Grassroots. An Editorial. R. H. CHAMBERLAIN. *Radiology*, December, 1959, 73: 927–928.

Under arrangement with a commercial roentgenographic safety group, about 100 members of the Philadelphia County Medical Society have availed themselves of a plan which provides comprehensive inspection and analysis of fluoroscopic apparatus. A cost of approximately $40 per machine includes a written report of the findings and recommendations, but does not include alterations unless they are so simple as to require no additional charge by the inspecting physicist. This appears to be a plan suitable for wide use. The problems of medical radiation control involve much more, of course, than correcting deficiencies in apparatus alone. Considerably more important are the methods of use of the apparatus and the judgment involved in choice of procedures for individual patients. These can be improved by educational methods which emphasize adequate dark adaptation before fluoroscopy, reduction in the time of fluoroscopic exposure, and limitation of fluoroscopy to situations in which it is specifically needed. Techniques of roentgenographic procedure should be evaluated critically. There is opportunity along these lines for constructive leadership at the grassroots as well as moral obligation to be of service in a field of special competence.—W. J. STEININGER

Mass Survey among Madrid Schoolchildren (in Spanish). J. M. MONTURIOL*. *Enferm Torax*, No. 31, 1959: 279–282. (* Inspección Médico Escolar del Estado, Madrid, Spain)

Of 7,859 children aged 4–13 years, 132 (1.67 per cent) were revealed to have active pulmonary tuberculosis, and 30 (0.18 per cent) rheumatic heart conditions.—Z. VIRÁGH

Studies on the Correlation between the Viability of BCG Vaccine, the Vaccinal Lesion, and the Tuberculin Allergy Induced by Vaccination in Humans. Report II (in Japanese). Y. OBAYASHI*, T. SAWADA, G. KUCHIKI, C. CHO, J. KAWASAKI, Y. INOUE, and S. OTA. *Kekkaku*, January, 1960, 35: 16–17. (* Kekkaku Yobokai, Kiyose, Tokyo, Japan)

The writers report on the results of analysis on the correlation between the number of viable units of BCG vaccine and the size of the vaccinal lesion (size of the scar 4 months after inoculation) in humans. A definite positive correlation ($r = 0.572$) was found between these two factors. A

positive correlation ($r = 0.316$) was also found between the average size of the vaccinal lesion and the postvaccination tuberculin reaction in the groups of children inoculated with vaccines of different viability. However, this correlation was less when compared with that between the two former factors.—I. TATENO

Detection of Pulmonary Tuberculosis in Subjects with Negative or Dubious Tuberculin Reactions (in Japanese). T. YOSHIOKA*, T. TANABE, and H. SUDO. *Clin Resp Organs*, January, 1960, 15: 44–46. (*Kekkaku Yobokai, Tokyo, Japan)

The writers attempted to diagnose patients with pulmonary tuberculosis from subjects whose tuberculin reactions were either negative or dubious. Of the 12,696 school children examined from 1953 through 1956, 6,886 fell into the category of the writers' study subject. Indirect roentgenographic examinations were made on all of them, and 6 cases (0.08 per cent) were detected. The tuberculin reactions turned positive in all 6 a month later. The writers considered the current school health regulation, requiring indirect roentgenographic examinations of all school children irrespective of their tuberculin reactions, an adequate procedure for detecting the maximal possible number of tuberculous patients.—I. TATENO

The Origin of The Term Anthracosis. A. MEIKLEJOHN*. *Brit J Industr Med*, September, 1959, 16: 324–325. (*U. of Glasgow, Scotland)

Dust diseases of the lungs are classified generically as the pneumoconioses. There are several varieties, of which anthracosis was the first to be named specifically. The original article, in which the name anthracosis was coined, is reprinted, prefaced by a biographic note on its author. The original article, entitled "Case of Anthracosis or Black Infiltration of the Whole Lungs," by Thomas Stratton, appeared in the *Edinburgh Medical and Surgical Journal*, 1838, *49:* 490. The term itself was used to mean charcoal lung, not black or coal lung, and was used by Dr. Stratton to describe the appearance of the lungs of a coal miner seen at autopsy. The author refers to his previous paper in the present journal (1951, *8:* 127) in which he traced the development of the pertinent nomenclature from melanosis to spurious melanosis and, finally, to anthracosis.—H. SIMON

BCG Vaccination. Leading Article. *Tubercle*, December, 1959, 40: 477–478.

In the *British Medical Journal* of June 6, 1959, there appeared an article titled "The Case Against BCG." It was by no less than 17 authors, all from the U. S. A. In the summary it was stated that: "An adequately controlled study of BCG among people living in their homes has never been accomplished. It has been found impossible." No evidence was produced for either of these statements. The clinical trial of the British Medical Research Council was briefly described; but no valid reasons were given for not classing it as "an adequately controlled study." The claim that such trials have been found impossible was apparently based on the undocumented opinions of "workers at Oxford University" and "Medlar, and others." The "impossible" has, of course, been achieved.

In this issue of *Tubercle*, three papers demonstrating the value of BCG vaccination are cited. This collection of papers is not "the case for BCG." That BCG vaccination under certain conditions can protect against tuberculous illness is proved, and the evidence has been published. There is no room for "cases" for or against an established fact. It is the practical application of this preventive method in changing circumstances in different countries that requires critical study and further experiment.—M. J. SMALL

BCG Vaccination in Man. T. M. POLLOCK*. *Tubercle*, December, 1959, 40: 399–412. (*Holly Hill, Hampstead, London, England)

In the American trials of Palmer and his associates, although each contained an adequate control group, protection was estimated from the notification rates and the participants were not followed up. This difference in procedure, rather than the epidemiologic or other considerations, might account for the lower degree of protection observed in this trial as compared with the other investigations. Therefore, it does not follow from the recent American findings that the scope for BCG vaccination is necessarily less in communities in which low degrees of naturally acquired tuberculin sensitivity are frequent. But the matter may well merit further investigation, e.g., in some tropical communities.

An indication of the contribution likely from mass vaccination of a single age group in communities with advanced public health and medical services has been given by the Medical Research Council trial of tuberculosis vaccines (Medical Research Council, 1959). This investigation began in 1950 and is still in progress. Approximately 56,700 school children entered the investigation during their last term at secondary modern schools in 1950, 1951, and 1952, when most were 14 years of age. In the first 5 years after entry to the trial, 153 cases of tuberculosis were found in the negative unvaccinated group, and 27 in the BCG-vaccinated group, an annual incidence of 2.30 and 0.38 per 1,000, respectively. The incidence of tuberculosis in the vaccinated group was thus only about $\frac{1}{6}$ the rate in the negative unvacci-

nated group. In the circumstances of the trial, vaccination with BCG thus conferred a substantial measure of protection against tuberculosis. The protection conferred by vole vaccine was of a similar order.

It has been suggested that the contribution made to the reduction of the total incidence of tuberculosis in the community is so small that mass vaccination is not worth while. A clearer indication of the value of mass vaccination is given by basing the appraisal of its worth on the expected incidence of tuberculosis which would, in the absence of vaccination, accumulate in the tuberculin-negative group. When this incidence is relatively large, as in present-day England, vaccination is clearly desirable; when, as is likely to happen in England at some future date, the incidence is small, the place of mass vaccination requires to be reconsidered. Comparisons of the decline in the total tuberculosis rates between communities in which BCG has been used and those where it has not have not suggested that any apparent advantage accrues from vaccination; this might seem to indicate that the vaccine is of little value in practice. However, social and epidemiologic differences make such comparisons between communities of doubtful validity. Moreover, it must be remembered that an appreciable decline in tuberculosis rates may occur in the vaccinated age groups without greatly affecting the total tuberculosis rates in the entire community.

An undoubted disadvantage of mass vaccination is the production of tuberculin sensitivity and the consequent interference with case finding by routine tuberculin testing. Tuberculosis incidence may be effectively reduced without the employment of vaccination in communities in which the sources of infection can be rapidly discovered and effectively isolated. However, the proportion of tuberculin-sensitive children in England is probably too great to make such a measure practicable on a large scale for some years to come. Taking all of the above considerations into account, an appraisal of the American criticisms indicates that objections to the safety of BCG are not substantiated by extensive practical experience, nor should its general efficacy as shown by the clinical trials of the vaccine be seriously considered to still be in doubt. In contemporary England, BCG can make a unique and important contribution to the reduction of tuberculosis in young adults. —M. J. Small

BCG Vaccination and Tuberculosis in Birmingham: A Study of Notifications Related to Vaccination of Children Before Leaving School. V. H. Springett*. *Tubercle*, December, 1959, 40: 432–442. (*U. of Birmingham, England)

BCG vaccination of Birmingham school children has reduced their tuberculosis notification rates by something between 0.5 and 0.7 per 1,000 per annum. Statistically, the evidence is of such a nature that it cannot be taken as establishing the value of BCG vaccination. Practically, and taken in conjunction with the strictly controlled Medical Research Council Trial, the evidence fully justifies the use of BCG in children about to leave school in Birmingham and similar communities. Financially, the cost of BCG vaccination in Birmingham is less (and probably much less) than the estimated cost of dealing with the cases prevented (Author's summary).—M. J. Small

An Estimation of the Scope for BCG Vaccination in Preventing Tuberculosis among Those Aged 15–19 Years in England and Wales at the Present Time. I. Sutherland*. *Tubercle*, December, 1959, 40: 413–424. (*Medical Research Council, London, England)

The second report of the Medical Research Council trial of tuberculosis vaccines in adolescents (Medical Research Council, 1959) contained an estimate of the benefit to be expected from BCG vaccination. If all the tuberculin-negative 14-year-olds had been vaccinated with BCG on entry to the trial in 1950–52, the reduction in the incidence of tuberculosis in the ensuing 5 years would have been 59 per cent. The present study, by taking into account the recent decrease in risk of exposure to tuberculous infection in England and Wales, provides similar estimates of the scope for BCG vaccination which are more up to date and, also, applicable to the whole country. Of the tuberculosis notifications among those aged 15–19 years in England and Wales in 1958, it is estimated that 52 per cent could have been prevented by BCG vaccination of all 14-year-olds who were then tuberculin negative. This estimate for 1958 is compared with that for 1953, which was 60 per cent. There has thus been a moderate decline in the scope for BCG vaccination during these 5 years.

In terms of the numbers of cases preventable by BCG vaccination of children aged 14 years, the scope has declined very considerably—from about 2,950 notifications among those aged 15–19 years in 1953, to 1,400 in the same age group in 1958. We may in a few years reach a situation in Britain in which mass vaccination of older school children prevents only small numbers of cases of tuberculosis in adolescents. It is suggested that a central bureau should be established to collect and interpret the information in connection with the official vaccination scheme. This could make a valuable contribution to the eradication of tuberculosis from Britain.—M. J. Small

The Use of BCG Vaccine in Mantoux-Positive and Mantoux-Negative Persons in East Africa. C. G. I. Gordon* and J. H. Shelley. *Tubercle*, December, 1959, 40: 425–431. (*Tuberculosis Hosp., Kibongoto, Northern Province, Tanganyika Territory, East Africa)

The object of this survey was to find out whether or not BCG vaccination can be safely undertaken without preliminary tuberculin testing. A group of 1,750 African children in northern Tanganyika were tuberculin tested (Mantoux test with 10 TU of OT). Four days later all were vaccinated intradermally with 0.1 ml. of freeze-dried BCG vaccine (Pasteur). The children were examined after 72 hours and again after 7 weeks. Pre-vaccination tuberculin reactions less than 5 mm. in diameter appeared in 1,610 children. In 223 (14 per cent) of these, there was a local reaction 72 hours after vaccination ("Koch reaction"), 35 of the reactions being 15 or more mm. in diameter. Pre-vaccination reactions of 5 or more mm. in diameter appeared in 140. No early local reaction to vaccination occurred in 11; the remaining 129 (92 per cent) reacted, 113 having reactions of 15 mm. or more in diameter. Of the 352 who had "Koch reactions," there were no visible reactions in 20 per cent after 7 weeks, ulcers were present in 20 per cent, local abscesses in 6 per cent, enlarged nodes in 10 per cent, and scars or cutaneous nodules in 49 per cent. Of the whole group of 1,750, 53 per cent had no visible reaction to vaccination when examined after 7 weeks. There were ulcers in 10 per cent, local abscesses in 3 per cent, enlarged nodes in 5 per cent, and either scars or cutaneous nodules at the vaccination site in 30 per cent.

The dangers of vaccinating individuals with tuberculin sensitivity demonstrated by the 10 TU Mantoux test seem to have been exaggerated; but if vaccination is done without preliminary tuberculin testing, there will be an increased number of early reactions and persisting skin lesions. These are more irritating than dangerous.—M. J. Small

Influenza Vaccination, Reaction Rates, and Absentee Experience. A. Mangelsdorff* and P. Kriedt. *AMA Arch Industr Health*, July, 1959, 20: 28–35. (*Prudential Insurance Co. of America, Newark, New Jersey)

The pandemic of Asian influenza had its peak throughout the country in October and November, 1957. The absentee rates of a company that did not give the vaccine, compared with those of a company that gave the vaccine late, and with another company that gave the vaccine early, demonstrate the effectiveness of the early vaccination program. The peak incidence of influenza and of colds did not coincide in most of the cities. The number of reactions to the influenza virus vaccine which were reported was high, but the duration and severity of the reactions were low. The rate of occurrence and the severity of reactions reported by women were greater than among men. The severity and duration of reactions were tempered by increasing age in the employee (after authors' summary).—T. H. Noehren

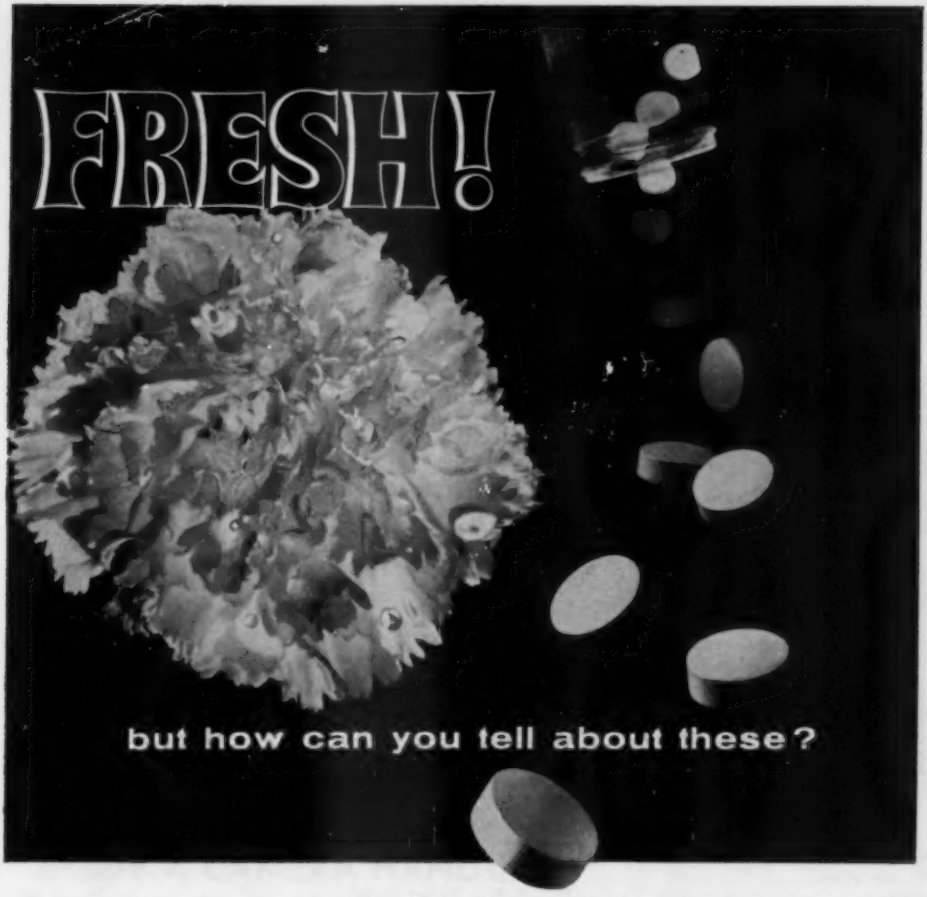
Aspergillosis. A Review and Report of Twelve Cases. S. Finegold* and J. Murray. *Amer J Med*, September, 1959, 27: 463–481. (*U. of California Med. Center, Berkeley)

The clinical and pathologic data in 12 cases of aspergillosis are presented. Eleven patients came to autopsy; 1 is still living. One of the patients had primary aspergillosis; the others all had secondary involvement. The 11 patients with secondary aspergillosis all had debilitating underlying diseases and had received antimicrobial therapy, usually multiple drugs, for a prolonged period. Six of these patients had received adrenocortical steroids or corticotropin. Three were leukopenic. Similar cases of aspergillosis from the literature, in which the use of antimicrobials and/or steroids may have played a role, are tabulated. Possible predisposing causes other than these are listed.

A new classification of aspergillosis is presented. The diagnosis of aspergillosis is difficult. Early diagnosis would probably improve results of medical treatment. Surgery is effective in drainage of abscesses and resection of localized lesions. Prophylaxis through more judicious use of antimicrobials and steroid hormones is most important, even though the use of drugs and steroids may be unavoidable; in these situations one should be alert to the possibility of superimposed Aspergillus (as well as other fungous and bacterial) infection (after authors' summary).—T. H. Noehren

Results of Tuberculin Testing and Radiography of 13-Year-Old Birmingham School Children from 1954 to 1958. W. L. Gordon*. *Tubercle*, December, 1959, 40: 466–467. (*Public Health Dept., Birmingham, England)

When BCG vaccination of 13-year-old school children was started in Birmingham in 1954, 18.3 per cent were found to give a reaction of 5 mm. or more induration to 10 TU of PPD intradermally. This figure has declined year by year to only 11.9 per cent in 1958. It is the practice that children who have a particularly strong Mantoux reaction have a chest roentgenogram without delay. It soon became obvious that the vast majority of cases of roentgenographically manifest tuberculosis were to be found in the strongly positive tuberculin reactors.—M. J. Small



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United States	4,651
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PHYSICIANS

SPECIALTY

	No.	%
No specialty	50	11.46
Starred pulmonary specialist	84	19.27
Pulmonary specialist	24	5.50
Starred internist	85	19.49
Starred surgeon	31	7.10
Surgeon	3	.68
Starred thoracic surgeon	27	6.19
Starred radiologist	7	1.60
Starred public-health specialist	5	1.14
Starred pathologist	3	.68
Starred pediatrician	3	.68
Starred otologist	2	.45
Starred and unstarred specialists in allergy, bacteriology, gastroenterology, hospital administration, industrial medicine, OALR, OBG, orthopedic surgery, physical medicine—one each	9	2.06
No information	17	3.89
	350	80.19
Institutional subscribers	86	19.72
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Full-time medical-school staff	7	1.60
Hospital administration	2	.45
Special research	1	.22
General public-health practice	10	2.29
Retired	3	.68
Not in practice	1	.22
No information	17	3.89
	350	80.19
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AGE OF PHYSICIAN

	No.	%
No information	17	3.89
No age given	1	.22
30–34	10	2.29
35–39	55	12.61
40–44	58	13.30
45–49	50	11.46
50–54	51	11.69
55–59	37	8.48
60–64	35	8.02
65 and over	36	8.25
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POPULATION

	No.	%
Under 10,000	56	12.84
10–25,000	39	8.94
25–50,000	44	10.10
50–100,000	38	8.71
100–200,000	32	7.33
200–500,000	48	11.00
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1	1	1	0	1	2	2	50–100,000
2	0	1	1	0	0	2	100–200,000
3	6	0	0	0	1	4	200–500,000
4	3	2	0	0	1	0	500–1,000,000
2	4	1	1	2	0	6	Over 1,000,000
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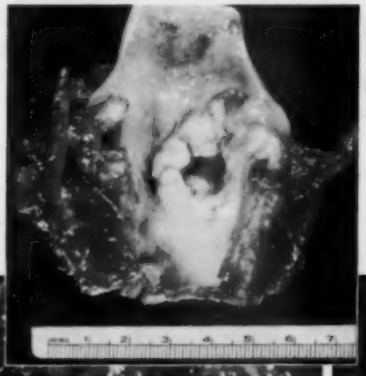

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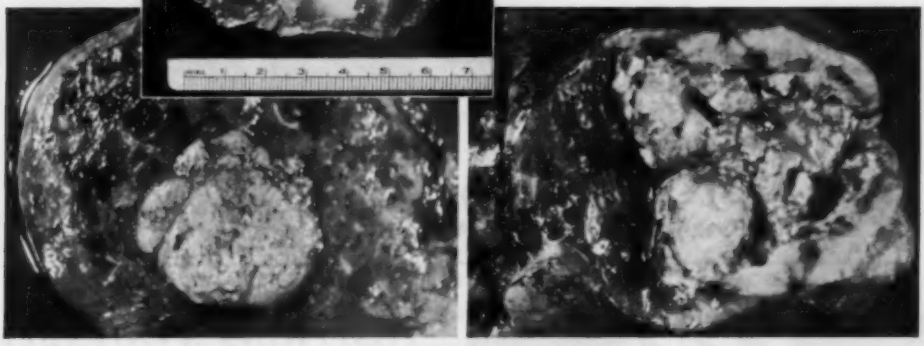

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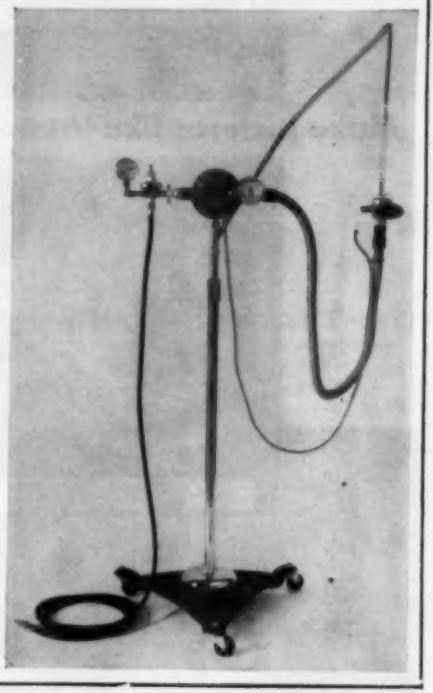

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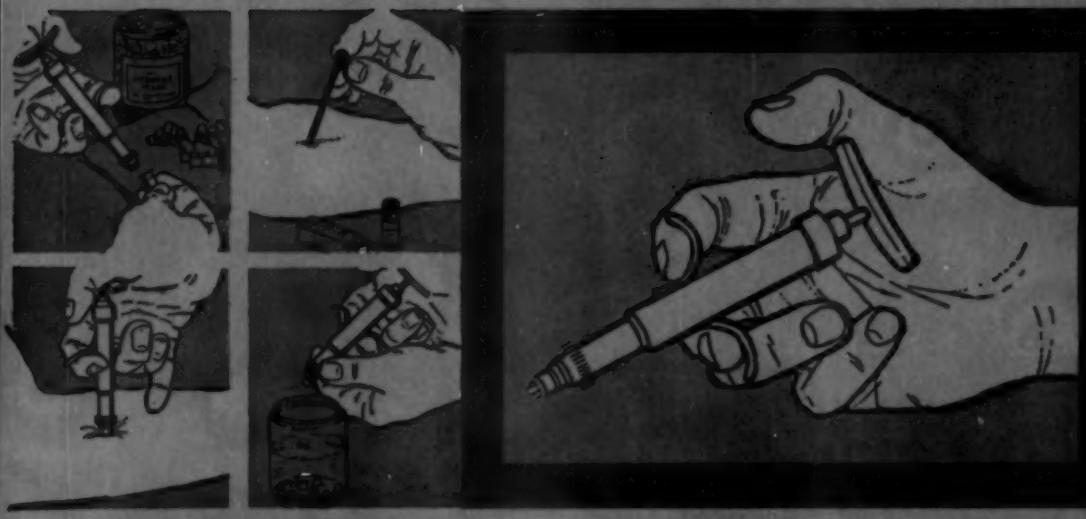

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